

American Journal
of
Digestive Diseases
Volume 15

The American Journal of
DIGESTIVE DISEASE

An Independent Publication

DEVOTED TO GASTRO-ENTEROLOGY AND NUTRITION

ORIGINAL CONTRIBUTIONS

- CREATININ — *H. L. Popper, M.D.* -----
- CONTRIBUTION TO THE DIAGNOSIS OF ACUTE PANCREATIC NECROSIS—*K. F. Herfort, M.D.* -----
- CHRONIC HEPATITIS: A LABORATORY REVIEW — *S. M. Rabson, M.D.* -----
- INDICATIONS AND CONTRAINDICATIONS FOR GASTROSCOPY — *Harry Barowsky, M.D.* -----
- CHRONIC AMEBIASIS: A GASTROSCOPIC STUDY — *Theodore C. Afendulis, M.D.* -----
- TECHNIQUE FOR PREVENTING LEAKAGE OF GASTROSTOMY AND ENTEROSTOMY — *Alexander Strelinger,*

- DIET AS A FACTOR IN HEADACHES — *John A. Turnbull, M.D.* -----
- CHANGES OF THE COLON SECONDARY TO CHRONIC ULCERATIVE COLITIS — *Thomas M. Johnson, M.D. and*
G. Orr, M.D. -----
- PREVALENCE OF OCCULT BLOOD IN THE STOOL—*W. D. Paul, M.D. and H. E. Hamilton, M.D.* -----
- DIETS -----
- REVIEW: -----
- TECHNIQUES IN DAILY PRACTICE — *White and Geschickter* -----
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Now More Than Ever The Physician's Advice Is Needed

Much confusion has resulted in the public's mind because of the conditions prevailing in the food field. Lessened food availability, the need of many people to economize, and the desire to cooperate with the government's aim toward world-relief, may well lead to deterioration of the nutritional state, unless competent guidance is offered.

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Volume 15

March, 1948

Number 3

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in
the
management
of
simple
diarrheas

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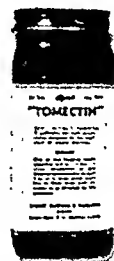
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- ¹ Malyoth, G.: Klin. Wchnschr. 13:51, 1934.
² Bittner, J. E., Jr.: Northwest Med. 35:445 (Dec.) 1936.
³ Myers, P. B., and Rouse, A. H.: Am. J. Digest. Dis. 7:39 (Jan.) 1940.
⁴ Powers, J. L.: Bull. National Formulary Committee 9:5 (Oct.) 1940.
⁵ Bloek, L. H., Tarnowski, A., and Green, B. L.: Am. J. Digest. Dis. 6:96 (Apr.) 1939.
⁶ Morrison, L. M.: Am. J. Digest. Dis. 13:196 (June) 1946.

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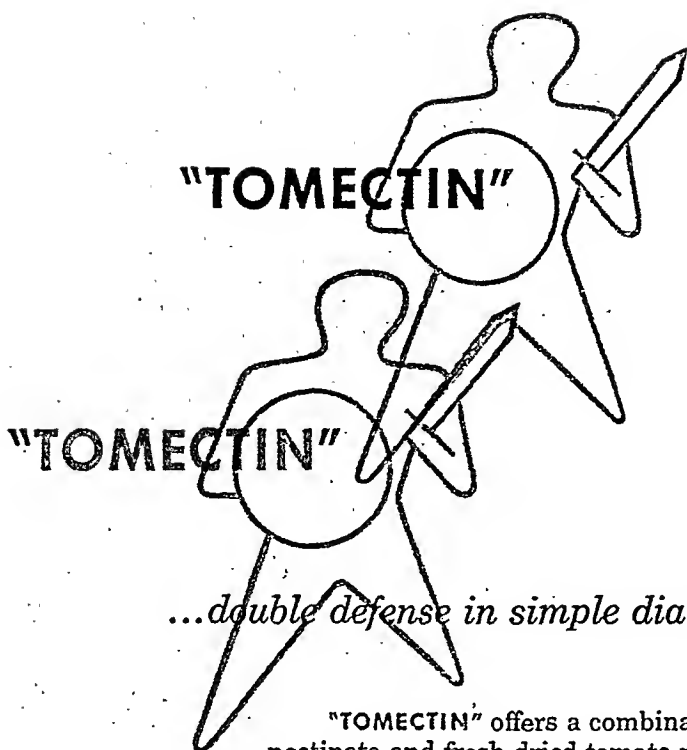
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¹Block, L. H., Tarnowski, A., and Green, B. L.: *Am. J. Digest. Dis.* 6:96 (Apr.) 1939

²Morrison, L. M.: *Am. J. Digest. Dis.* 13:196 (June) 1946

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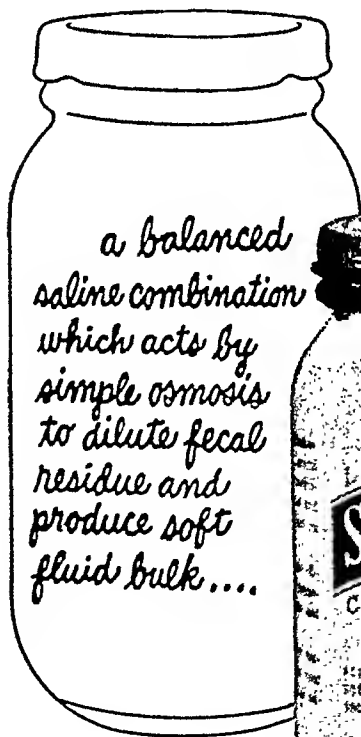
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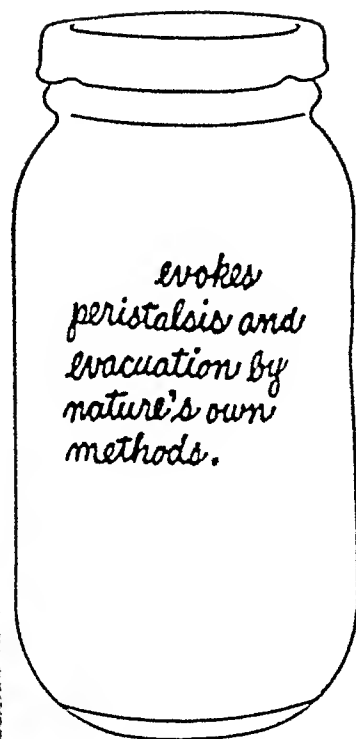
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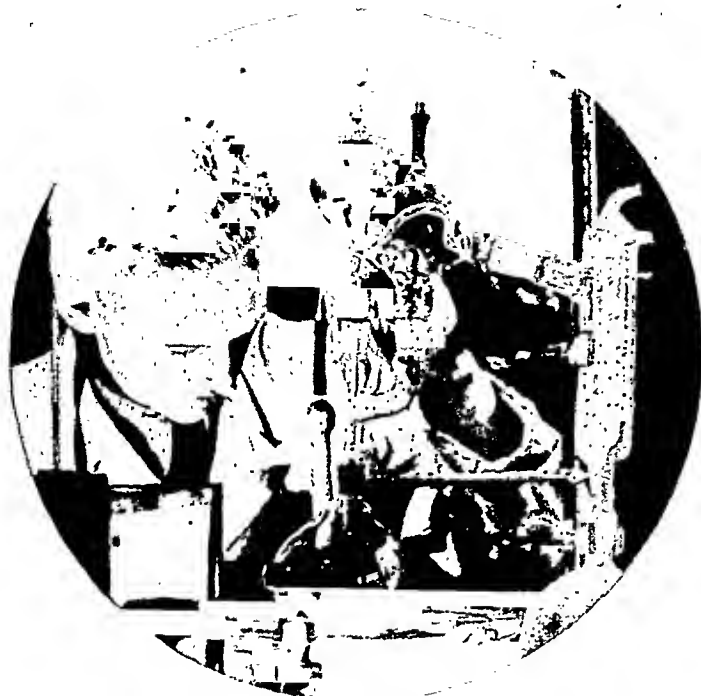
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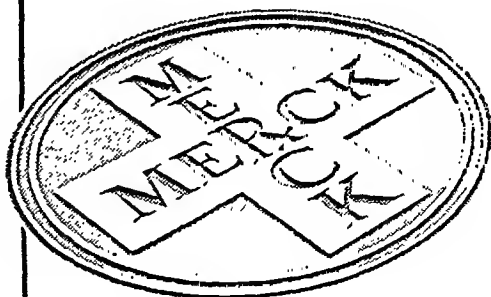
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44...

OF NEMBUTAL'S CLINICAL USES

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Cardiovascular

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Coronary disease¹
Angina¹
Decompensation
Peripheral vascular disease

Endocrine Disturbances

Hyperthyroid
Menopause—female, male

Nausea and Vomiting

Functional or organic disease (acute
gastrointestinal and emotional)
X-ray sickness
Pregnancy
Motion sickness

Gastrointestinal Disorders

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Pylorospasm²
Spasm of biliary tract²
Spasm of colon²
Peptic ulcer²
Colitis²
Biliary dyskinesia

Allergic Disorders

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Irritability Associated With Infections⁴

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Chorea
Hysteria
Delirium tremens
Mania

Anticonvulsant

Traumatic
Tetanus
Strychnine
Eclampsia
Status epilepticus
Anesthesia

HYPNOTIC

Induction of Sleep

OBSTETRICAL

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Eclampsia
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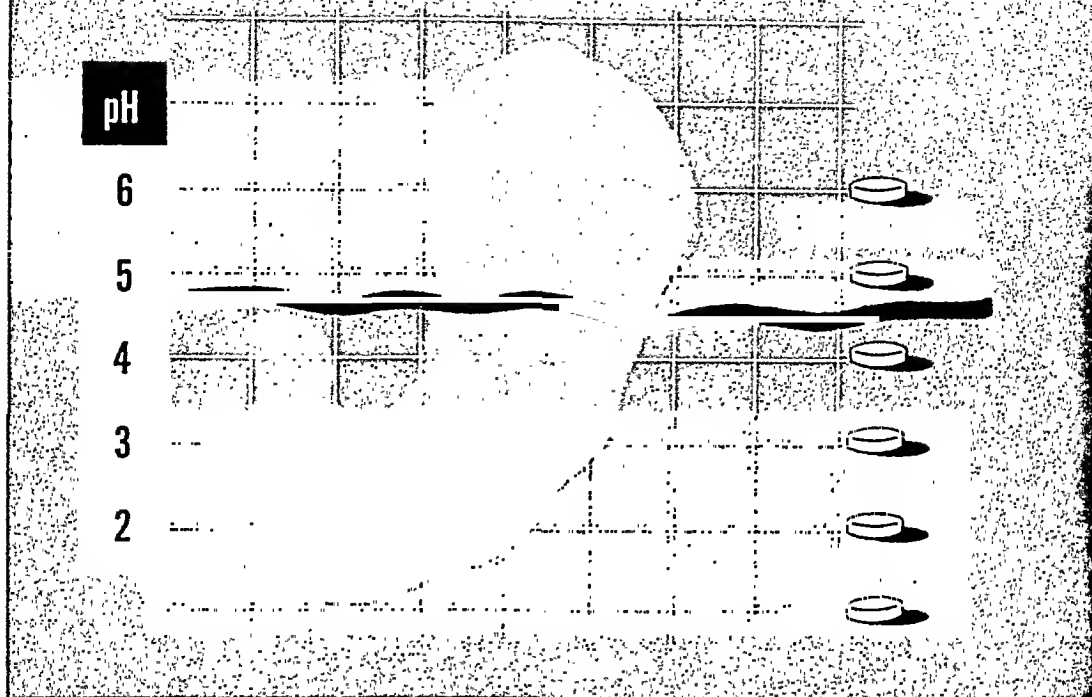
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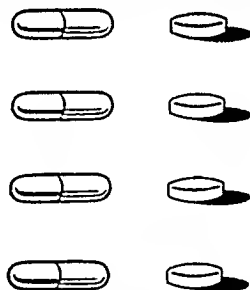
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Acute Pancreatitis

An Evaluation of the Classification, Symptomatology, Diagnosis and Therapy

By

H. L. POPPER, M.D.

CHICAGO, ILLINOIS

THE FIRST REFERENCE to the clinical entity, now known as Acute Pancreatitis, was made in 1882 when Balser (1) described fat necroses. Fitz in 1889 (2) gave the first comprehensive description of acute hemorrhagic pancreatitis. The incidence of this condition is not exceptionally rare. Hamperl e.g. in 1933 (3) reported 67 cases of acute pancreatitis in 22,577 autopsies, which is 0.3%, or one in 337 necropsies. Yet, a correct clinical diagnosis is made only in a rather small number of cases. There is no doubt that our diagnostic results can be improved by being pancreatitis conscious clinically, and by using the appropriate laboratory tests.

Acute pancreatitis is difficult to classify into simple pathologic conditions as it is neither an outspoken inflammatory or infectious process, nor a purely necrotizing or hemorrhagic lesion, though it may be a combination of all these processes at the same time. It is a pathologic entity in itself, differing from the pathology of other organs because of the peculiar physiologic and biochemical properties of the pancreatic gland.

Acute pancreatitis is the comprehensive name for all the acute disorders of the pancreas, but such terms as: acute pancreatic necrosis, hemorrhagic pancreatitis, edema of the pancreas, interstitial pancreatitis, transient pancreatitis, fat necrosis of the pancreas, etc., are used in accordance with the pathology or the clinical course.

For the purpose of discussion, it is best to divide acute pancreatitis into the mild and severe forms. The gross pathology in the mild cases is usually a glassy edema of the pancreas and of the peripancreatic tissue, often extending into the mesocolon or into the root of the mesentery, with varying amounts of slightly bile colored or slightly hemorrhagic peritoneal exudate. A moderate amount of fat necrosis is often seen around the pancreas, in the root of the mesentery, or in the omentum. The terms "edema of the pancreas" or "interstitial pancreatitis" are applied to these mild forms and, in the very mildest type, the term transient pancreatitis is used.

In the severe cases large amounts of usually markedly hemorrhagic, less often bile colored intraperitoneal exudate, are found. Fat necroses are frequently seen all over the abdomen and even in remote areas; the pancreas is swollen and either studded with fat necroses

or the area of the pancreas is transformed into a bluish-black mass. On sectioning this mass, one often sees that the pancreas is much less hemorrhagic than it looks from the outside and that only part of the pancreas is hemorrhagic or that the hemorrhagic mass consists only of peripancreatic tissue. In other cases the pancreas is completely hemorrhagic and necrotic. According to the prevailing pathology in each case, the condition is called either hemorrhagic pancreatitis, hemorrhagic necrosis, apoplexy of the pancreas, pancreatic necrosis, or fat necrosis of the pancreas.

The question whether these two types are different entities or only different stages of the same process has not yet been settled. I believe that they are different stages of the same process, for we frequently saw cases showing the typical edema of the pancreas at operation, which showed necrosis of the pancreas at necropsy, a few days later. Furthermore, the same pathogenic mechanism could be demonstrated in all forms of acute pancreatitis (4). It seems rather probable that pancreatitis, like all other diseases, has mild forms as well as severe ones, and that sometimes a mild form turns into a severe one. However, there is no question that not all cases of acute pancreatitis start with edema, for real severe cases often show a necrosis of the pancreas from the beginning. The differentiation between mild and severe forms is of practical clinical importance, but the clinical symptoms and the pathological changes do not always run parallel. Thus, not so rarely clinically severe cases will show only relatively minor changes of the pancreas.

The etiology of acute pancreatitis is fairly well understood, though there are controversial views regarding certain points. It is generally agreed that acute pancreatitis is due to the action of activated pancreatic juice upon the pancreas itself. This juice is activated by the change of inactive trypsinogen into trypsin by such substances as duodenal juice, bile, bacteria, active trypsin, and by many other media, and even spontaneous activation of trypsinogen may take place. In addition to trypsin, lipase plays a major role.

Thus pancreatitis is caused by the action of protein and fat splitting enzymes on the glandular tissue, a fact that explains the unusual features of acute pancreatitis.

Activated trypsin alone cannot start any pathology in the pancreas. The normal intestinal tract contains activated trypsin all the time, and I could demonstrate the presence of activated pancreatic juice in the normal biliary tract in many cases (5). In animal experiments, we were able to demonstrate that a diffusion of pancreatic enzymes through the intact duodenum occurred if a mixture of pancreatic juice and bile was allowed

From the Department of Gastro-Intestinal Research, Research Institute, Michael Reese Hospital, Chicago.

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to accumulate until the organ became distended (6). In analogy, if activated pancreatic juice accumulates under pressure in the pancreatic gland, it will diffuse into the interstitial tissue of the pancreas and then into the peripancreatic tissue. Such a process would give us a picture very much like that of edema of the pancreas. We could demonstrate, in fact (7), the presence of large amounts of pancreatic enzymes in the edema fluid of animals, thus proving that edema of the pancreas is not an inflammatory edema but rather an accumulation of diffused pancreatic juice in the intra- and peri-pancreatic tissues. Whether rupture of small ducts (Rich and Duff) plays a role in pancreatitis has been questioned by the author (8).

Part of the edema fluid is absorbed rapidly into the general circulation and accounts for increased blood enzyme values which we found in animal experiments, sometimes as early as five to ten minutes after damaging the pancreas (9). Another part of the edema fluid diffuses out of the pancreas, producing free fluid in the peritoneal cavity which contains large amounts of pancreatic enzymes, as we could demonstrate in animal experiments as well as in the clinical cases (8). Thus, pancreatic enzymes come in contact with the intra-abdominal tissues and fat necrosis occurs by the action of lipase on fat tissue.

That explains the development of edema of the pancreas and of acute pancreatitis with fat necrosis, but not the severe forms, because retention of activated pancreatic secretions does not seem to cause hemorrhagic or necrotic lesion of the pancreas. However, we were able to show, in not yet published experiments, that temporary occlusion of the pancreatic artery, which otherwise has no effect on the pancreas, will cause necrosis of the glandular tissue in the presence of edema of the pancreas. It seems that decrease in cell resistance caused by this temporary interruption of the blood supply is providing the additional factor necessary for destructive action of trypsin on the pancreatic tissues.

The mechanism of retention of activated pancreatic juice is in the majority of cases due to a common channel. Common channel formation as first suggested by Opie (10) in 1901, denotes an anatomical variation in which occlusion of the papilla of Vater will block the outflow of bile and of pancreatic juice into the duodenum, but will allow a free communication between both ducts behind the obstruction. This block may be caused by a small stone or by spastic contraction of the sphincter of the papilla, as pointed out by Archibald (11). The numerous anatomic investigations performed to determine the incidence of a common channel in normal cases are not unequivocal. Rienhoff and Pickrell (12) reported recently that in 18% of their 250 dissections a complete block at the papilla would have converted the two ducts into a communicating system. Leven (13) in cholangiographic studies succeeded to show filling of the pancreatic duct following injection into the common bile duct, thus proving common channel formation, in 23% of his cases. On examination of 200 specimens of gall bladder bile of surgical cases without affection of the pancreas, mostly cases of cholelithiasis, I found in 20 cases or

10%, pancreatic enzymes in the gallbladder bile, thus proving that in 10% of these cases not only a common channel was present, but that an actual reflux of pancreatic juice into the bile tract had taken place (14). In contrast to the 10% incidence noted in the 200 cases with normal pancreas were the findings in 18 cases with present or past acute pancreatitis, including mild as well as severe cases. In 16 of these 18 cases or in 89%, common channel formation was demonstrated.

In 60-80% of cases of acute pancreatitis, associated pathology of the biliary tract is found which can account for the block at the papilla. However, I was able to show that a reflux of pancreatic juice into the biliary tract had occurred even in cases of acute pancreatitis which showed no pathology of the biliary tract. That means that even in absence of any visible pathology of the biliary tract, as found in 20 to 40% of the cases of acute pancreatitis, a spasm of the sphincter of Oddi with formation of a common channel might be the causal mechanism of the acute pancreatitis. In 10 to 25% of the population, the possibility of common channel formation is present. If in such people the outflow is blocked at the papilla and if the mixture of pancreatic juice and bile remains in the communicating system under increasing pressure, then the stage is set for development of an acute pancreatitis (5). This process would explain the presence of a pancreatitis in 16 of the 18 cases in my series. In the remaining two cases other unknown etiologic factors must have been at work.

The clinical picture of acute pancreatitis is not characteristic, either in history, complaints, or in physical findings. Some features, however, are prevalent; and therefore, should be suggestive of pancreatitis. The disease is extremely rare in children but has been reported in all other age groups. Some statistics show a greater incidence in men, some in women. In my series women were definitely predominant. Some cases are obese but a good many are not. Some are alcoholics, many are not. A history of previous gallbladder attacks or of epigastric pain can be elicited in more than half of the cases. The patients are often subicteric, but as a rule have no distinct jaundice.

The most characteristic complaints are severe pain in the epigastrium radiating to the left side and to the back. This pain follows an episode of indigestion of a few days duration or may come on suddenly, not so rarely after a heavy meal. One must not wait for the textbook description of an excruciating pain not relieved by morphine to make the diagnosis of acute pancreatitis. The majority of cases have just very severe pain that is not easily distinguished from the other painful abdominal or renal conditions. However, the radiation to the left is diagnostic. There is often repeated vomiting without ensuing relief. The vomitus is uncharacteristic, containing food particles first, followed by gastric juice and bile. Usually from the onset of the attack, the passage of gas and of stools is interrupted.

On physical examination, three types of cases can be found. 1). Severe, toxic cases which present a

shock-like picture. They have marked tenderness and some rigidity all over the abdomen, but more pronounced in the epigastric region, and they have a high pulse rate and occasionally show mottled cyanosis of the abdomen or limbs. These cases look very much like acute vascular accidents such as coronary occlusion or embolism of the mesenteric vessels, or they may appear like some overwhelming infection. 2). Cases with predominantly peritoneal symptoms. The marked tenderness and marked rigidity will make differentiation from perforated peptic ulcer difficult, but the rigidity rarely attains the board-like quality of a perforation. This group comprises mild and severe cases and an early separation of the two forms is often not possible. 3). The third clinical form is characterized by intestinal paresis as the predominant symptom. These cases show very little rigidity but some tenderness and a gradually increasing distention of the abdomen. They are usually light cases with rather limited constitutional symptoms. These cases look very much like renal or intestinal colics.

The laboratory findings are of greatest value for the diagnosis of acute pancreatitis. Urinalysis frequently shows albumin with various types of cylinders, especially in severe cases. Glycosuria is seen in five to 20% of the severe cases, but rarely in the mild cases. Traces of bilirubin are found occasionally in the urine and increased urinary urobilinogen is seen rather frequently. Blood examination often reveals a white blood count of around 20,000, with polymorphonuclears predominating. The N. P. N. and urea are at upper normal limits and are often markedly elevated in severe cases. There is frequently a slight elevation of the icteric index. The fasting blood sugar is above normal in many cases and as a rule markedly increased in the severe forms (15). Glucose tolerance tests, though they regularly show abnormal curves, are not advisable in acute cases. Edmondsen and Berne (16) have recently reported a decrease of serum calcium in 36 of 50 cases of acute pancreatitis which seemed to be in proportion to the amount of fat necrosis.

The most significant finding in acute pancreatitis is an increase of serum amylase and lipase, that can be found very shortly after the beginning of the process. However, this increase lasts only a few days and then a gradual return to normal takes place, regardless of the process in the pancreas. The increase of amylase can be demonstrated in the urine too, but variations in kidney function make the blood test more reliable. The increase of serum amylase and lipase is due to absorption of pancreatic enzymes into the general circulation. We could show in animal experiments that this absorption takes place mainly by way of the portal vein and to a lesser extent through the thoracic duct (9), and we could demonstrate that these absorbed enzymes are eliminated rapidly from the blood (17); that shows that the blood-enzyme-level presents the actual balance of the continuously absorbed enzymes minus the continuously eliminated enzymes. Therefore, in acute pancreatitis, a constant inflow of large amounts of enzymes must take place, to keep the blood level high despite the constant elimination. In a severely

damaged pancreas, enzyme production decreases and finally stops, and therefore not enough enzymes are absorbed to maintain a high blood level. This explains the drop in blood enzyme levels after a few days, even though a progressive process may be taking place in the pancreas. Therefore, it is important to do the enzyme test as soon as possible, for a negative test is of very little significance several days after the onset of the process.

The usual lipase determination takes 24 hours; the amylase test can be done in less than an hour and is therefore, of more practical value in acute cases. Increase of blood amylase is, with few exceptions, limited to acute pancreatic processes. It is sometimes seen in gallstone attacks and occasionally, though only to a small degree, in cases of peptic ulcers penetrating into the pancreas and in acute parotitis (18, 19). Thus the serum amylase test, properly performed and evaluated, will give us the means to make the quick diagnosis of acute pancreatitis in the majority of cases. It is an interesting and not too well known fact that amylase values are usually higher in the less severe cases and highest in edema of the pancreas, while only moderately elevated in pancreatic necrosis. In contrast, the fasting blood sugar is not at all or only little above normal in mild cases and is increased in proportion to the extent of the process in severe cases. Agren and Lagerlof's secretin test (20), and the pancreatic function test elaborated in animal experiments in our laboratory (21, 22), are not suitable for cases of acute pancreatitis, for they are based on stimulation of the pancreatic secretion, which will aggravate the pathologic process in the pancreas.

Until recently acute pancreatitis was considered a surgical emergency and either incision with drainage of the pancreas or, in later years, drainage of the gallbladder or common duct was performed. The mortality of these procedures ranged around 50% as reported, e.g., in Schmieden's review of 1,728 cases, treated surgically (23). Gradually a change to conservative treatment has occurred with an impressive reduction of the mortality rate, and only a few experts still favor surgical treatment. An important disadvantage of surgery in severe cases is also the rather frequent incidence of wound disruption, formation of a pancreatic fistula or of complicated wound infections with much prolonged sickness. Exploration probably causes no harm in mild cases with doubtful diagnosis, if manipulation of the pancreas is avoided and the operation is terminated, possibly with gallbladder drainage, as soon as the condition is recognized. In contradiction to Elman's view (24) that surgery of the severe cases may benefit occasionally a doomed patient, one can say that many more hopeless looking cases can be saved with proper conservative treatment than with surgery. However, conservative management can be applied safely only when the diagnosis is correct beyond any doubt and when all real surgical emergencies have been ruled out completely.

The proper conservative therapy has as its aim to diminish the secretory activity of the pancreas and to relieve spasm of the sphincter of Oddi. This can be

achieved by avoiding any stimulation of the pancreas, by active inhibition of the pancreatic secretion and by spasmolytic medication. Anything that stimulates the vagus nerve will stimulate the pancreas; therefore, prostigmine, as well as morphine or its derivatives, should be excluded. The vagotonic action of morphine might conceivably be the reason for the often mentioned insufficient pain relief after morphine administration in acute pancreatitis. Hyperglycemia has a pronounced stimulating effect by way of the cholinergic mechanisms, and hypoglycemia has a marked vagotonic action too. Parenteral glucose administration as well as the regulation of the blood sugar by insulin must therefore be handled extremely carefully. In order not to provoke secretin stimulation of the pancreas the patient should not get anything by mouth. Continuous suction should keep the stomach empty and prevent hydrochloric acid from entering the duodenum. To inhibit pancreatic secretion, ephedrine and repeated doses of atropine are indicated. Demerol with its atropine-like action is probably the analgesic of choice and should be given instead of morphine. Nitro-glycerine (25) and other spasmolytics might be of some value.

Intravenous fluids should consist mainly of saline solution and blood-plasma. Glucose should be given only with repeated checks of the blood sugar and combined with atropine.

Attempts have been made to influence the course of the disease by paralyzing the intraperitoneal en-

zymes by inhibitor substances such as quinine or, as we have tried, by detergents. These experiments were unsuccessful so far. Some rather impressive clinical results were reported several years ago with the oral administration of large amounts of alcohol (26). It might be worth while to try intravenous administration of alcohol.

In 1931 and 1933 I reported (27, 28) encouraging diagnostic results in seven cases with paravertebral block on the left side at the level of the eighth to tenth thoracic spinal processes. In four of these cases the block had not only a diagnostic but also a remarkable therapeutic effect. The pain did not return to any appreciable degree after the novocaine effect had worn off, and the patients remained free of symptoms. This curative effect, which can only be expected in not too severe cases, may in part be due to the decrease in pancreatic secretions and to a release of arterial spasm following interruption of sympathetic pathways to the pancreas, but it may likewise be due to inhibition of the sphincter of Oddi, providing release of backed up secretions.

Recovery from one attack of pancreatitis does not preclude the possibility of further attacks. To prevent recurrences, it seems best to have the patient avoid heavy, rich meals, or any food that might irritate the bile tract. In cases with biliary tract pathology, cholecystectomy and removal of stones from the bile ducts seems advisable after a proper interval, because this will eliminate a possible cause of further attacks.

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Contribution to the Diagnosis of Acute Pancreatic Necrosis

By

K. F. HERFORT, M.D.
PRAGUE, CZECHOSLOVAKIA

THE DIAGNOSIS of the diseases of the glandular part of the pancreas offers many difficulties. The methods employed in the functional examination of the external pancreatic secretion are still suffering from lack of sensitivity. Such tests are helpful only in more extensive pancreatic disturbances and prove to be unreliable even in such cases. It was hoped that the determination of amylase in blood and urine, originated by Wohlgemuth at the turn of the century, might be of value in overcoming diagnostic difficulties. No agreement, however, has been reached as yet as to the reliability of this examination. Some authors consider the determination of amylase very useful as a functional test of the glandular part of the pancreas, while others point out the discrepancies between the results of amylase determinations and the objective clinical findings (1, 2, 3, 4, 5, 6, 7). In our experience, certain diagnostic conclusions can be made if amylase is increased in blood and urine on repeated examinations. In a variable number of cases, however, the amylase determinations do not give a conclusive result. The method used for amylase determination certainly cannot be blamed for these discrepancies because it is very simple and easily carried out. We are inclined to suppose that the cause of the divergent results lies in the localization of the pathologic process in the pancreas, causing different amylase excretion in diseases of the same origin and even of the same intensity.

The determination of the pancreatic ferments in the duodenal secretion is a great asset to the functional examination of the pancreas. The technical methods used for the stimulation of the external secretion of the pancreas lag far behind those used in the examination of the gastric juice. The author of this paper believes that this is the chief setback in the utilization of the analysis of the duodenal secretion which is a reliable indicator of this function of the pancreas. Pathologic changes in the glandular apparatus of the pancreas do not affect all enzymes equally in every case.

Chiray and Bolgert (8, 9) and Herfort (10, 11, 12) used such findings in the diagnosis and in the causative analysis of pancreatic disorders. A functional examination of the pancreas, however, cannot be carried out in a patient with grave symptoms, as are usually present in acute pancreatitis.

X-ray examination offers information only when the pancreas is so enlarged that it causes an alteration in the location or shape of the neighboring organs. Furthermore, the X-ray examination does not permit a decision as to whether the enlargement is of in-

fectious or of neoplastic origin. Pancreatic stones, however, are easily discovered by X-rays. The findings of Ludin and Schneidegger (13), Bedrna and Sixe (14) and Kemp-Harper (15) proved the value of X-ray examinations in pancreatic stones and the frequency of such calculi.

Our present report deals with acute pancreatic necrosis. When faced with the differential diagnostic implications of the picture, we believe that the vehemence of the initial symptoms, the sudden onset and the gravity of the clinical signs are most characteristic for acute pancreatic necrosis. Very often, however, cases of sudden abdominal disturbances are met in which acute pancreatic necrosis is suspected but the clinical picture is not clear-cut. The need for a reliable method of laboratory examination is keenly felt in such instances. As it was shown above, such a diagnostic aid has not been found as yet. The search for auxiliary diagnostic methods is impaired by the lack of clinical material. Jirasek (16) of the General Hospital of Prague found among 2,957 patients operated during the period from 1927 to 1936 only 12 (0.4%) cases of acute pancreatic necrosis.

While studying the case histories and autopsy reports of 29 patients suffering from acute pancreatic necrosis who were treated in the hospitals of the Charles University of Prague*, striking changes of the white blood count were observed, consisting of lymphopenia accompanied in most cases by leukocytosis but often presenting a normal or decreased total number of white blood cells. Surgical and autopsy findings in some of these cases, including the cell counts and the percentage distribution of the white cells are shown in the following:

1). B.H., 65 y. On operation: pancreas edematous, in some spots jelly-like, with hemorrhages of different size. Many stones in the gall-bladder. W.B.C.: 16,700 Eos 4. Bands 18, Segments 57, Lym 10, Mono 11.

2). M.L., 72 y. On operation: Pancreas of the size of two fists, edematous with small hemorrhages and numerous foci of fatty necrosis. 30 gall-bladder stones. W.B.C.: 12,400 Eos 1, Bands 21, Segments 60, Lym 8, Mono 11.

3). J.F., 49 y. On operation: Much hemorrhagic fluid in the abdominal cavity. Enlarged, hemorrhagic, jelly-like pancreas. 22 gall-bladder stones. W.B.C.: 16,500 Bands 15, Segments 69, Lym 6, Mono 10.

4). V.S., 42 y. On operation: Enlarged tail of the pancreas, with extensive steatoses. Fine and coarse stones in the gall-bladder. W.B.C.: 12,800. Bands 14, Segments 65, Lym 11, Mono 10.

5). A.K., 63 y. On operation: Swollen, edematous

From the First Medical Department of the Charles University, Prague, Czechoslovakia.
Submitted July 23, 1947.

* The author is indebted to Drs. Jirasek, David and Niederle for their kind cooperation and permission to use this material.

pancreas with numerous steatoses but few hemorrhages. 8 large gall-bladder stones. W.B.C.: 10,700. Eos 2, Bands 14, Segments 64, Lym 11, Mono 9.

6). V.M., 41 y. On operation: Swollen and edematous tail of the pancreas, with numerous steatoses but few hemorrhages. W.B.C.: 11,920. Bands 15, Segments 62, Lym 12, Mono 11.

7). J.U., 39 y. On operation: Swollen and edematous pancreas with numerous steatoses and hemorrhages. W.B.C.: 9,800. Bands 26, Segments 59, Lym 4, Mono 11.

8). A.M., 47 y. On operation: Hemorrhagic fluid in the abdominal cavity. Swollen, edematous and hemorrhagic pancreas. Autopsy report: Colliquation of the entire pancreas. W.B.C.: 18,600. Eos 1, Bands 37, Segments 53, Lym 7, Mono 2.

9). B.N., 61 y. On operation: Diffuse peritonitis and acute pancreatitis with cholelithiasis. W.B.C.: 21,700. Bands 12.8, Segments 80, Lym 1.6, Mono 5.6.

10). A.B., 54 y. On operation: Acute pancreatitis with cholecystitis and cholelithiasis. W.B.C.: 15,500. Eos 1, Bands 21, Segments 67, Lym 10, Mono 1.

11). J.S., 38 y. On operation: Acute pancreatitis and cholelithiasis. W.B.C. 18,500. Bands 12.8, Segments 76, Lym 5.6, Mono 5.6.

12). H.J., 37 y. On operation: Abdominal contusion. Pancreatic apoplexy. Hemoperitoneum. Fatty necrosis of the stomach and the Mesenterium. W.B.C.: 7,200. Eos 2, Metam 1, Bands 32, Segments 57, Lym 5.2, Mono 2.8.

13). D.B., 57 y. Autopsy findings: Acute necrosis of the pancreas. Numerous foci of Balzer's necrosis in the abdominal fat. Chronic cholecystitis and cholelithiasis. W.B.C.: 10,350. Eos 2.4, Myelo 2.4, Metam 3.2, Bands 32, Segments 44.8, Lym 8, Mono 7.2.

14). B.V., 49 y. Autopsy findings: Acute necrosis of the head of the pancreas. Cholecystitis and cholelithiasis. Numerous leiomyomas of the stomach wall. W.B.C.: 9,200. Bands 18.4, Segments 60, Lym 18.2, Mono 3.2.

15). V.F., 45 y. Autopsy findings: Hemorrhagic necrosis of the head of the pancreas. Cholecystitis and

cholelithiasis. W.B.C.: 13,650. Meta 5, Bands 60, Segments 34.

16). F.V., 37 y. Autopsy findings: Acute pancreatic necrosis. Cholelithiasis. W.B.C.: 4,900. Eos: 1.6, Bands 26.4, Segments 56, Lym 15.2, Mono .8.

17). Z.N., 41 y. On operation: Acute pancreatic necrosis. W.B.C.: 16,650. Bands 6.4, Segments 83.2, Lym 4.8, Mono 5.6.

DISCUSSION

Acute pancreatic necrosis has usually such grave effect upon the general condition of the patient that an examination of the duodenal juice directly or after Schmidt's meal is not possible. In some cases the so-called "distant symptoms", as affecting the left diaphragm and lung, do not arise. In others, the blood and urine amylase is not changed. Because of the lack of evidence, the diagnosis of acute pancreatic necrosis in such cases is not established until it comes to laparotomy or autopsy. An absolute lymphopenia was, however, present in all cases studied by us. This lymphopenia is especially helpful in establishing the diagnosis when the W.B.C. is normal or the amylase level is not significantly changed.

In an attack of cholelithiasis or nephrolithiasis, in acute perforation of a gastric or duodenal ulcer or in a myocardial infarction leucopenia is frequently present. Neither in a perforated gastric or duodenal ulcer, nor in an attack of nephrolithiasis of the left side, where the clinical onset sometimes resembles acute pancreatic necrosis, or in other acute abdominal conditions have we found lymphopenia.

We believe, therefore, that leukopenia with lymphopenia in an acute abdominal condition is a helpful aid in the diagnosis of acute pancreatic necrosis.

SUMMARY

Tests available at present for the investigation of the function of the glandular part of the pancreas are not always helpful in the diagnosis of acute pancreatic necrosis. Author found lymphopenia in 29 such cases. The diagnostic value of this observation is discussed.

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Jaundice and Hepatitis: A Laboratory Review

By

S. M. RABSON, M.D.

FORT WAYNE, INDIANA

THIS REVIEW attempts to hew a recognizable path through the accumulating literature on laboratory tests in jaundice and hepatitis. The attempt was instigated by the practical necessity of selecting tests which could be performed in a hospital laboratory limited in facilities and personnel.

It is fortunate that the growing practice of liver biopsy furnishes material for the closer correlation of organic, laboratory and clinical investigation. Hence, the discrepancies, hitherto so evident in this field, are slowly being explained if not eliminated. It need not be emphasized that whatever the tests selected, they must be carefully performed. A single test competently done, though not always too helpful, is at least not misleading. Numerous tests whose accuracy is questionable are wasteful of time and money, and serve only to becloud the conduct of the individual case.

Hepatitis describes liver changes of varied grade and extent. The least severe grade of the disease is represented by epithelial cell swelling, the presence of abnormal liver cells, lymphoid cell infiltration about the lobules, and sometimes frank necrosis of the liver cells. The most flagrant degree of hepatic damage is manifested in an intensification of the changes already described, as well as disintegration and disappearance of cord cells and proliferation of connective tissue. The causes of hepatitis include virus infection (epidemic hepatitis, acute catarrhal jaundice, transfusion hepatitis, etc.) usually following plasma transfusions or during epidemics.

Obstructive jaundice is less extensively discussed for several reasons. First, the etiological background is more readily understood. Second, radiological studies help greatly in its diagnosis. Finally, if the views of Lucke (3) are to be followed, the mechanism of jaundice in hepatitis is, after all, obstruction of the intralobular canaliculi. In fact, as Hanger (2) emphasizes, "obstructive jaundice of long standing may develop changes similar to those of hepatogenous jaundice;" this is the not infrequent observation of the pathologist at the necropsy table.

Hepatitis may be divided into three stages: pre-icteric, icteric or intermediate, and defervescent (final when fatal). Watson and Hoffbauer (5) subdivide the second stage into two phases of functional derangement: a). hepatocellular, with emphasis on liver cord cell disturbance, b). cholangiolar. "Cholangiolar" refers to the periphery of the hepatic lobule where the bile capillaries (lying in the cords) dilate as anapillae to empty into the perilobular or terminal bile ducts. The latter, in turn, communicate with the small bile ducts in the portal spaces or triads. The division into

hepatocellular and cholangiolar is not a precise one. The first may predominate earlier in the disease, and the second at a later stage. On the other hand, the division may merely emphasize one component at the expense of the other.

About twenty liver function tests are described in the publications under review. These, with their authors' normal standards, are presented in Table I. It must be remembered that there is some disagreement concerning normal values and their range, but this is becoming less common.

Acute hepatitis. According to Sherlock (4) the serum bilirubin rises during the acute icteric phase, but the elevation in serum phosphate is not as pronounced. Serum cholesterol is frequently within the normal range and is never greatly increased. The total serum proteins are usually normal, but the severe grade of hepatitis provokes a decrease, together with a drop in albumin. Galactose time varies from normal in the less severe state to an extended period in the histologically more powerfully affected. Hippuric acid synthesis apparently can not be closely correlated with the degree of liver damage.

In the period of recovery from acute hepatitis, serum bilirubin drops, but there is no constant rate of fall. Serum phosphatase levels take longer to reach normal values. Cholesterol occasionally rises, but only inconstantly. Total serum protein values do not change, but albumin rises, globulin falls, and the A/G ratio ascends. Galactose tolerance drops to normal, as does hippuric acid synthesis.

Sherlock concludes that the following tests are useful: serum bilirubin, total serum proteins and albumins, galactose time, and intravenous hippuric acid. The serum phosphatase is customarily less than 30, and serum cholesterol below 300.

TABLE I
LIVER FUNCTION TESTS: NORMAL VALUES

TEST	AUTHOR		
	Hanger	Sherlock	Watson & Hoffbauer
Bilirubin, total (T)	0.5-1.0 mg.	1 mg.	
Bilirubin, delayed reacting (T-I')	0.8-1.0 mg.		
Bilirubin, prompt reacting (I')	0-0.19 mg.		0.2 mg.
Bromsulphalein retention	0-10%		0-5%
Cephalin-cholest. flocc.	0 to +		
Cholesterol, total	160-240 mg	120-150 mg	200 mg.
Cholesterol ester fraction	65-75% of total		125 mg.
Coproporphyrin			100 gamma
Galactose clearance	75 min.	30-90 min.	
Hippuric acid synthesis	0.7 g.	0.75-1.2 g.	0.7 g.
Protein, total blood		6-8 g.	
Albumin, blood	4-5.6 g.	3.4-5 g.	4 g.
Globulin, blood	1.5-2.6 g.	1.5-3 g.	2.5 g.
Prothrombin time		12-18 sec.	12 sec.
Serum alk. phosphatase	2-4 units	5-10 units	4 units
Thymol turbidity	0-4 units		4 units
Urobilinogen in urine	1 unit		1 unit (3 mg.)

Department of Pathology, Saint Joseph Hospital, Fort Wayne 2, Indiana.

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Hepatic cirrhosis is divided by Sherlock into the histologically inactive and histologically active. In the inactive phase serum bilirubin is ordinarily less than 1, phosphatase and cholesterol as in acute hepatitis, galactose and hippuric acid tests normal, and total serum protein and albumin of no value. When the cirrhosis is active, the picture is the same except for elevation of the serum bilirubin which is commonly below 12.

The extent of damage and the assay of extent of surviving liver tissues are also evaluated by Sherlock. Serum bilirubin reveals high levels in severe lesions of acute hepatitis, but its determination in active cirrhosis is useless. She applies the word "index" to serum phosphatase, serum cholesterol, total proteins and the intravenous hippuric acid test as assessing instruments in both hepatitis and cirrhosis. In both diseases the serum albumin is usually less than 3 in very severe lesions, and galactose time (in minutes) is high in pronounced states.

Franklin and his associates (1) found no quantitative relation to diffuse liver cell damage with these tests: total cholesterol, total proteins, alkaline phosphatase and fecal urobilinogen. There was a little association with urinary urobilinogen, increase in sedimentation rate, serum non-protein nitrogen elevation, and decreased cholesterol ratio. A moderate relation was observed for prothrombin time decrease and serum vitamin A. Close correlations existed with cephalin cholesterol flocculation, thymol turbidity, bromsulphalein retention, and reversal of albumin-globulin ratio.

Regeneration of liver cells was related to thymol turbidity, but only questionably to cephalin flocculation and vitamin A. Thymol turbidity apparently remains abnormal longest and so is still positive at this period.

In cirrhosis, where lobular patterns are being reconstructed, the cephalin flocculation test was more often positive than any of the other methods employed. The sedimentation rate showed a moderate relation to the condition.

Hanger (2) states that in the pre-icteric phase of hepatitis, laboratory tests may be normal. A rise in alkaline phosphatase, bromsulphalein retention, positive cephalin flocculation and increased urine urobilinogen may point to liver disease before jaundice appears. Bilirubinuria, especially in morning specimens, may be noted before jaundice or hyperbilirubinemia; this is also remarked by Watson and Hoffbauer (5).

With the onset of icterus, the cephalin flocculation and thymol turbidity tests are positive. Urine urobilinogen falls, and serum phosphatase may rise. During defervescence laboratory tests may be positive because of the continued presence of the diseased tissues.

As a result of their division of hepatic derangement in different liver disease into the hepatocellular and cholangiolar categories, Watson and Hoffbauer (5) place emphases on different tests. In the hepatocellular disturbance there is increase of delayed reacting bilirubin and urinary urobilinogen. Galactose clearance, hippuric acid synthesis, serum albumin and cholesterol ester fraction are diminished. The cephalin

cholesterol flocculation and thymol turbidity tests are positive. For the cholangiolar type they increase of prompt reacting (1 minute) bilirubin, blood total cholesterol, and serum alkaline phosphatase. There is bilirubinuria, and bile salts are detected in blood and urine.

Watson and Hoffbauer state that testing for bilirubin in the urine is useful in the early stages of hepatitis. They recall that a hundred years ago bilirubinuria was mentioned occurring before icterus. As a matter of fact, bilirubin has been described as often evident in the urine before the total serum bilirubin has risen above 1 mg. The promptly reacting serum bilirubin which appears in 1 minute, is associated with the bilirubinemia. In delayed reaction the total serum bilirubin may be greater than 2 mg. without the detection of bilirubin in the urine. Because of these findings, Watson and Hoffbauer believe that only the total and the promptly reacting bilirubin are important, the difference between the two values (T-1) equals the delayed or indirect type. Most normal individuals have less than 0.1 mg. promptly reacting bilirubin per 100 cc. and the upper limit is about 0.2 mg.

In the period of defervescence of hepatitis, the urinary bilirubin disappears, despite relatively large amounts of promptly reacting bilirubin in the serum. This may be caused by alterations in the renal threshold.

The Watson and Hoffbauer paper is particularly valuable for its practical phases of laboratory procedure. They refer to a simple method for detecting bilirubin in urine. Barium chloride is used to impregnate strips of thick, specially retentive filter paper. A strip is inserted into the urine and held upright for a few moments so that the urine ascends by capillarity. The paper is removed and Fouchet's reagent dropped on the area corresponding to the surface zone of the urine. As little as 0.05 mg. bilirubin per 100 cc. of urine has been detected, but the green color customarily does not appear until 0.1 mg. Fouchet's reagent consists of 10 parts of a 25% aqueous solution of trichloroacetic acid and 1 part of 10% ferric chloride solution.

The Ehrlich test for urinary urobilinogen is also employed by Watson and Hoffbauer. They suggest that it be used serially by the same person. A faint pink is classified as a trace, and an intense red-blue as 4 plus. Because of variations during the day, and from day to day in the urobilinogen level, the test must be employed serially rather than haphazardly. The use of a saturated aqueous solution of sodium acetate intensifies the color of the reaction, and also minimizes the color produced by indole and skatole. The authors do not permit a patient to resume normal activity until the urobilinogen is at normal levels for several days.

Among the conclusions of Watson and Hoffbauer, as already stated, are the early appearance of bilirubinuria with a rise of promptly reacting serum bilirubin, and the early disappearance of bilirubin from the urine when total bilirubin is still elevated. In short, jaundice may persist, especially in the cholangiolitic type. Urinary urobilinogen (Ehrlich test) is positive early, but diminishes or disappears during the height of jaundice.

A positive test usually shows incipient improvement, but may occasionally be temporary or slight. A persistent Ehrlich reaction probably indicates continuing activity of the hepatitis. Urinary coproporphyrin is the last to fall to normal levels.

The cholesterol ester fraction declines emphatically early in the disease and is ordinarily low when serum bilirubin is highest. Bromsulphalein retention is early manifest and quickly pronounced. More than 5% retention after the disappearance of jaundice suggests persistent activity or danger of cirrhosis. Cephalin cholesterol flocculation and thymol turbidity tests are not positive as early as others and the turbidity method is slower as well.

In summary, Watson and Hoffbauer list those tests which are of most value for evaluating liver function in hepatitis. For the pre-icteric phase, serum bilirubin (particularly the prompt reacting), urine bilirubin, and urinary urobilinogen are best. When icterus has appeared, cephalin flocculation and thymol turbidity, serum total cholesterol and ester fraction, and serial Ehrlich tests are emphasized. In the late defervescent stage weight is given to serum bilirubin (especially delayed reacting), urinary urobilinogen, cephalin flocculation and thymol turbidity, bromsulphalein and coproporphyrin.

Watson & Hoffbauer (5), like Franklin and his associates (1) and Sherlock (4) have utilized liver biopsy to achieve a closer correlation between laboratory and clinic. However, the biopsy specimen is not necessarily helpful in determining etiology. As an example, the writer, on examining liver biopsy material in a recent

case of jaundice, stated that the picture was compatible with that of acute hepatitis. At necropsy a fortnight later, there were multiple small liver abscesses secondary to calculosis of gall bladder and common duct and severe ascending inflammation of the extra-hepatic bile passages. The abscesses were probably less than two weeks old, but even if they were not, the reason for the failure to find them in the biopsy specimen is readily understood. The lesions were well separated from each other and lay in a plane above that employed in biopsy. Further, even in diffuse liver disease, not all parts of the liver show the same degree of disturbance.

Tests for the determination of obstructive versus non-obstructive jaundice must obviously be interpreted very carefully. Table II summarizes what the more intrepid souls have chosen to present.

SUMMARY

In an attempt to determine which of the numerous tests offer the most aid in evaluating function in diffuse liver disease (hepatitis), several recent papers have been reviewed. There is general, but not always specific, agreement concerning the value of each of the score of methods employed. It is agreed, however, that, in general, some tests are of greater value in one phase of the disease than in another. Thus, the careful and painstaking compilation and integration of the clinical findings must precede recourse to laboratory aids. Thereafter, the intimate correlation of laboratory and clinic becomes increasingly important.

TABLE II
DIAGNOSTIC VALUE OF LIVER FUNCTION TESTS

TEST	HEPATITIS				OBSTRUCTIVE JAUNDICE	
	Franklin	Hanger	Sherlock	Watson & Hoffbauer	Hanger	Sherlock
Bile salts in blood and urine				Ch		
Bilirubinuria				Ch		
Bilirubin, total		+	O		+	O
Bilirubin, delayed reacting, increase		rapid +		H		
Bilirubin, prompt reacting, increase				Ch	slow +	
Bromsulphalein retention	++	+			+	
Cephalin-cholesterol flocculation	++	+		H	Neg.	
Cholesterol, total, increase	O	decrease	—300	Ch	+	O
Cholesterol ester fraction, decrease	±	+		H	Normal	
Galactose clearance, decrease			O	H	Normal	O
Galactose clearance, increase		+				
Hippuric acid synthesis, decrease		+	O	H	Normal	O
N. P. N., blood, increase	±					
Protein, total blood	O	—	O			O
Albumin, blood, decrease		+	O	H	Normal	O
Globulin, blood, increase		+			Normal	
A/G ratio, reversal of	++				Vit. K	
Prothrombin time, decrease	+	+				
Sedimentation rate, increase	±					
Thymol turbidity	++	+		H	Neg.	
Urobilinogen in urine, increase	±	+		H	Neg.	
Urobilinogen in feces	O					
Vitamin A	+					

Franklin. ++, close relation; +, moderate; ±, little; O, no relation.

Hanger. +, positive; —, decrease; Neg., negative.

Sherlock. O, no diagnostic value.

Watson & Hoffbauer. H, positive in hepatocellular phase; Ch, positive in cholangiolar phase.

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Indications and Contraindications for Gastrosocopy

By
HARRY BAROWSKY, M.D.
NEW YORK, N. Y.

GASTROSCOPY has gained prominence as a diagnostic procedure in determining gastric disease. The valuable contribution which this type of examination has made is largely due to the development of the flexible gastroscope. However, it must be emphasized that other types of gastroscopic instruments still have some value.

Gastrosocopy as it is employed today may be divided into three categories. The first is the popular and widely used lens system flexible gastroscope. The second is the rigid open tube variety; although limited in its usefulness, there still is a definite need for this type of examination. The third is a retrograde instrument which can only be used in patients with gastrotomies.

THE FLEXIBLE GASTROSCOPE

The flexible gastroscope has, by far, made the greatest contribution in the evaluation of gastric pathology. However, it still should be considered only as a useful adjunctive procedure. This type of examination of the stomach does not in any way replace the need for other methods of diagnosis. It is important to do a

careful history, physical examination, x-ray study, gastric analysis and any other laboratory procedures that may be necessary. In most instances, a satisfactory diagnosis is made by these methods alone. However, in some cases, these procedures will fall short of establishing the underlying pathology. It is in these patients, that gastrosocopy should be employed.

The indications for this procedure may be divided into three groups. First, where routine studies failed to reveal a positive diagnosis of gastric disease. Second, as a supplementary aid to x-ray diagnosis. Finally, to follow the course of benign gastric lesions which may become malignant.

1. When routine studies fail to reveal any diagnosis (Chart I)-in patients complaining of the following:

a. Epigastric pain. In these cases, there is a strong tendency to relegate the patient to the functional dyspepsia group. However, in a good many such instances, gastrosocopy may reveal chronic gastritis and occasionally, small gastric tumors or ulcers or posterior wall pathology.

b. Hematemesis. In this group, gastrosocopy may find a small bleeding peptic ulcer, tumor or diffuse bleeding from the gastric mucous membrane; the latter is occasionally seen in some types of gastritis or blood dyscrasias.

c. Malignant Syndrome. When patients present the

From the Department of Medicine, Section of Gastroenterology, New York Medical College, Flower and Fifth Avenue Hospitals.

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CHART I

GASTROSCOPIC FINDINGS IN PATIENTS WHERE
ROUTINE STUDIES FAILED TO REVEAL A DIAGNOSIS

	Types of Gastritis							Other Findings
	No. Cases Studied	No. Normals	No. Gastritis	% Gastritis	Atrophic	Superficial	Hypertrophic	
Epigastric pain	372	190	172	46%	27	56	59	6 Peptic Ulcers 4 Polyps
Hematemesis	28	23	2	7%	1	1	0	1 Bleeding Ulcer 1 Benign Tumor 1 Small Ca
Malignant syndrome	22	17	3	14%	2	1	0	1 Lympho-sarcoma 1 Ca Posterior wall
Total	422	230	177	42%	30	58	59	

symptoms of weight loss, anorexia and asthenia, gastroscopy should be employed. Even though no gastric symptoms may be present, carcinoma of the posterior wall or shallow malignant lesions such as lymphosarcoma may have been overlooked by the ordinary diagnostic methods.

2. Gastroscopy as a supplementary aid to x-ray diagnosis. Occasions arise where x-ray interpretation of stomach lesions may need further corroboration. Although in a majority of instances, x-ray diagnosis is fairly accurate, it must be stressed that situations arise when roentgen interpretation is difficult, indefinite and may at times be erroneous.

Positive findings: Gastroscopy should be employed as a control when a positive x-ray diagnosis of gastric neoplasm is made. Several benign conditions present x-ray deformities which are indistinguishable from cancer: The most common of these is antral gastritis. The inflammatory reaction and edema being largely confined to the antrum will produce a prepyloric narrowing and irregularity. Hypertrophic gastritis, especially when advanced may become polypoid. Under such circumstances, it will mimic extensive adenocarcinoma by producing "finger printing" defects. Less frequent affliction but just as difficult to distinguish are gastric syphilis, tuberculosis, Hodgkins and Boeck's Sarcoid. They may produce gastric defects which simulate neoplasm of the stomach.

Other changes which may at times make roentgen interpretation difficult or indefinite are imbedded foreign body or bezoar, an unusual mucosal fold, perigastric adhesions, persistent spasm and occasionally benign tumor or extrinsic pressure.

Furthermore, it should be emphasized that if gastric neoplasm is present this type of examination is not entirely wasted. The gastroscopist will not only confirm it but will be able to give added information as to the type and extent of involvement so that if resection is contemplated, this additional knowledge will be of value to the surgeon.

Negative findings: Negative x-ray interpretation should not always be considered as a final diagnosis. If, clinically, gastric carcinoma is suspected, gastroscopy should be employed. An error in roentgen diagnosis may be made when the carcinoma is small or flat. Under the circumstances, no definite defect is produced by the barium contrast media and negative findings are usually reported. Lesions situated on the posterior wall of the stomach may not be visualized when ordinary x-ray technic is used. This is due to the fact that frequently a stomach is overloaded with the barium mixture and the heavy column of barium situated in front of the tumor screens it from view. However, it must be acknowledged that some of these tumors may be elicited when proper pressure and rugae studies are done.

b. Gastroscopy, as an aid in differentiating between benign and malignant gastric ulcers: A common request that is frequently made of the gastroscopist is to determine whether a gastric ulcer is benign or malignant. Occasionally, this distinction is extremely difficult, since it has been demonstrated many times that a peptic ulcer may have all the morphologic characteristics of being benign to the roentgenologist, to the gastroscopist, to the surgeon at laparotomy and to the pathologist on gross examination. Yet, on microscopic section, evidence of malignant changes may be found. Furthermore, it has been pointed out that occasionally, a carcinomatous ulcer may appear to heal completely under medical therapy. Such phenomena are contrary to general belief and will mislead the clinician as to the true diagnosis. Fortunately, this type of difficulty is not encountered too frequently. In the average case, differentiation between the classical benign and malignant gastric ulcers can be made, since they each have distinct features. In Table II are the criteria upon which a differential diagnosis between a benign and malignant gastric ulcer is made gastroscopically.

c. To help clarify the etiology of pyloric obstruction. In most instances in this condition, the stomach

TABLE II

Characteristics	Differential Diagnosis Between	
	Benign Peptic Ulcer	Carcinomatous Ulcer
1. Site	It is situated on a flat surface	Usually it is situated on an elevated area
2. Shape	It is deep, punched out crater-like in appearance	Frequently it is "bowl" shaped and shallow
3. Margin	Its margin is well defined in its entire circumference	Its margin is round, sloping and generally does not form a complete circumference
4. Floor—Its Color	The floor is gray to a whitish yellow. Occasionally brown and after a hemorrhage, dark red	The floor may be of many colors. Usually it appears necrotic and is dark brown or dirty gray in color
5. Floor—Its Structure	The floor is generally even and flat	The floor is irregular, nodular and has ridges. Pieces of necrotic tissue may be observed
6. The surrounding area	The surrounding mucosa ordinarily is normal, sometimes it may be inflamed. However, it is flexible.	The surrounding mucosa in advanced stages is somewhat nodular and appears stiff and infiltrated. Its color is at times a pale red

is markedly dilated. On x-ray examination, the barium sinks to the most dependent portion of the stomach and prepyloric area is usually not well filled out.

3. To follow the course of benign tumors, polyps, gastric ulcers and chronic gastritis, especially the atrophic variety, repeated gastroscopic examinations are indicated. First, to determine whether proper healing is taking place and second, to be on guard for possible malignant degeneration.

OPEN TUBE GASTROSCOPE

The Open Tube Gastroscope is a straight metal instrument. It does not differ very much from that which had been used by the pioneers of gastroscopy. However, it fulfills a definite need. The popular types in use today are the Janeway and Jackson open tube gastroscopes. They are similar in structure to the esophagoscope.

It requires training and skill to be able to examine a patient with this type of instrument. Serious complications which may prove fatal will occur if this procedure is not done properly. The dangers result from trauma or rupture of the esophagus. These complications are mediastinitis, mediastinal abscess, mediastinal emphysema, gaseous cervical cellulitis, subcutaneous emphysema and pneumothorax.

The procedure is similar to esophagoscopy. It is done under direct vision. The object is to find the lumen of the esophagus and follow it. The preparation of the patient and the application of surface anesthesia is the same as for gastroscopy with the flexible instrument. Some operators will often use general anesthesia for this type of examination.

The indications for its use are the following:

1. Removal of foreign bodies from the stomach. When the foreign body is too large to pass through the pylorus and it is not of a character to cause perforation, a waiting period of one month is considered safe. When the object has sharp points or edges or has toxic qualities, it should be removed immediately.
2. For obtaining a biopsy from the proximal area of the interior of the stomach. Since this procedure is not entirely free from danger, it should be resorted to only when it is essential to determine the nature of the lesion in this area.
3. Supradiaphragmatic stomach. If pathology is sus-

pected in this area, the open tube gastroscope should be employed, for the hiatal hernia of the stomach cannot be distended sufficiently to obtain a satisfactory view with the side vision of the flexible instrument.

RETROGRADE GASTROSCOPY

The retrograde gastroscope is markedly limited in its usefulness. It can only be employed in those patients having a gastrostomy.

The chief indication for the use of this instrument is for palliative treatment of advanced neoplastic disease for which the gastrostomy has been performed. This is especially true for lesions at the "cardia." Therapy is carried out by the insertion into the tumor of radon seeds by means of a gold radon seed carrier. Another contribution that this instrument makes is that biopsies of the interior of the stomach can easily be obtained with the use of a biopsy forceps. Furthermore, observation of the progress of the disease can also be recorded.

CONTRAINDICATIONS FOR GASTROSCOPY

Since technical difficulties and hazards have been practically eliminated, the contraindications to gastroscopy are almost identical to those for the passage of the ordinary Ewald tube. The history and physical examination as well as the fluoroscopic study of the esophagus and mediastinum, usually will determine the contraindications.

The following lesions within or about the esophagus will interfere with the passage of the instrument and may cause perforation or hemorrhage: They are — Obstruction of the esophagus by tumor or stricture; Diverticula of the esophagus; Obstruction of the cardia by stricture or tumor; Aneurism of the aorta; Esophageal web, and varices of the esophagus.

Advanced cardiovascular disease. The added stress of gastroscopy may prove detrimental in the following: Cardiac decomposition; Coronary disease, and marked hypertension.

Marked debilitating diseases. The added strain of this procedure may prove harmful in: Advanced pulmonary disease; fever, and peritonitis.

Other conditions in which caution should be resorted to are: Kyphoscoliosis; Epilepsy, and jaundice without proper vitamin K preparation.

Gastritis and Amebiasis: A Gastroscopic Study

By
THEODORE C. AFENDULIS, M.D.
ATHENS, GREECE.

VARIOUS DISCOMFORTS of the stomach are well known to appear during amebiasis and often constitute the sole clinical symptom.

Many cases of amebiasis which give the clinical picture of peptic ulcer, chronic gastritis etc. are described in literature as well in everyday experience. In Greece such cases are not rare.

Patients often complain of nausea, lack of appetite, as well as a feeling of burning at the epigastrium, followed by acid regurgitation and a feeling of weight. More seldom they complain of pain of various intensity, sometimes regardless of meals.

As far the intestine is concerned, patients do not complain of discomfort and usually stools are normal. On the other hand, sometimes dysenteric disturbances whether recent or old are mentioned in the patients' history.

By physical examination, one usually finds signs of amebiasis, namely sensitiveness of the large intestine especially the sigmoid and the descendent which is spastic and can easily be distinguished as an elastic cord under the examining hand.

It is very difficult for patients to realize that such disturbances are secondary to amebiasis whether latent or in evolution. However, the result of the examination of the stool, as well as the special antiparasitic treatment forces them to realize the real cause of their illness. In our Clinic a great number of cases of amebiasis were treated during the past few years.

Many of these cases came to the hospital complaining of discomfort in the stomach for which they had been treated from time to time with no positive result. Other patients complained additionally of intestinal disorders.

In some of these cases we proceeded to make a detailed examination of the stomach as far as its state and functions are concerned. X-rays, examination of the gastric juice and the flexible gastroscope of Wolf-Schindler were used for the thorough examination of the stomach.

Altogether we examined 25 patients. Cases of combination of peptic ulcer and amebiasis, which are very common, are not included. Eighteen of the twenty five patients showed symptoms of chronic gastritis discovered with the gastroscope. Only a few case reports will be given.

CASE REPORTS

Case 1 : P.V., Age 20, male R.N. 159. Typhoid fever at 7 years. Little use of nicotine. For more than a week complains of epigastric distress followed by stool with mucus

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and blood, feeling of weight at the epigastrium with acid regurgitation, especially after meals.

Examination of stool proved vegetative forms cysts of histological ameba.

Gastric juice : Maximum values of acidity; free HCl 60; Total acidity 70.

Gastroscopy : At the anterior and posterior wall of the stomach red patches surrounded by pale mucosa. Folds a little swollen. Supersecretion of mucus. Pyloric region not well described.

Diagnosis : Chronic superficial Corpus gastritis with hyperacidity.

Case 2 : G.A., Age 29, male, R.N. 303. Three years ago dysenteric disorders, diagnosed as amebiasis. For the last five years periodical gastric disorders, namely light epigastric distress followed by regurgitation and giddiness. Examination of stools proved the existence of vegetative forms of histolytic ameba.

X-Ray : pylorospasmus of medium intensity.

Gastric juice : free acid 26; total acidity 36.

Gastroscopy : Red pigment spots of mucosa of the body and pyloric antrum. Folds swollen at certain parts. Supersecretion of mucus.

Diagnosis : Chronic superficial gastritis with normal gastric acidity.

Case 3 : St.D., age 26, female, R.N. 547. Typhoid fever during childhood. Menstruation normal. For the last 5 months complains of acid regurgitation and epigastric distress immediately after meals. In the stool existence of cysts of histolytic ameba.

X-Ray : Nothing of importance.

Gastric juice : free acid 72; total acidity 80.

Gastroscopy : The mucosa of the body of the stomach at the anterior and posterior wall near the lesser curvature, is swollen with small nodular proliferations. Folds somewhat thickened. Supersecretion of mucus.

Diagnosis : Chronic hypertrophic Corpus gastritis with hyperacidity.

Case 4 : M.B., age 25, male, R.N. 25. For the last 4 years gastric disturbances and regurgitations. Periodically diarrhea, with mucus. Examination of stools : vegetative forms of histolytic ameba.

X-Ray : Negative.

Gastroscopy : In the body of the stomach folds thickened, tortuous with dusky red mucosa. At the lesser curvature nodular hyperplastic processes, size of a small lentil, surrounded by a red halo.

Diagnosis : Chronic hypertrophic Corpus gastritis with hyperacidity.

Case 5 : K.D., age 28, male, R.N. 534. Fifteen years ago infectious jaundice. Little use of nicotine and alcohol. For the last two years complains of acid regurgitations, feeling of weight and light periodical pain at the epigastrium. Examination of stools proved cysts of histolytic ameba.

X-Ray : Negative.

Gastroscopy : Mucosa especially at the body of the stomach thin and pale. Pyloric antrum normal. At the body and especially at the posterior wall small red patches as well as a small erosion, surrounded by congested mucous membrane.

Diagnosis : Chronic atrophic Corpus gastritis with combination of superficial gastritis and anacidity.

DISCUSSION

It is already known that gastritis is often a complication of amebiasis. *Letulle* was the first to describe

such a case, during which he even found amebae by histological examination.

On the other hand, Baumel, Huard, Speder, Doukas etc. studied the clinical symptoms of gastritis. They believed that hypoacidity and anacidity were the cardinal cause of gastric trouble. Very few gastroscopic studies have been made, according to our references. *Gutzeit* and *Teitge* describe a case of a woman who for years suffered from amebic colitis. The gastroscopy showed atrophy of the mucosa with chronic superficial gastritis of the pyloric antrum. *Doukas*, 1940, described three cases of chronic amebiasis with hypertrophic gastritis of the body of the stomach. In the first of the above three cases the secretion of the gastric juice was normal, in the second it was hypoacid and in the third anacid.

Gastroscopically, we have found nearly all vari-

eties of chronic gastritis, from superficial gastritis to hypertrophic and atrophic gastritis.

As far as the secretion of the gastric juice is concerned, we found hyperacidity, or normal values, or hypoacidity, or anacidity either histamin refractory or not.

The diagnosis of the combination of gastritis and amebiasis in most cases is also interesting from a practical point of view. As far as the cause of the above mentioned gastritis, we believe that it is an endogenous one.

However, whether this gastritis is due to the influence of toxic products of amebae on the mucosa of the stomach, or of toxins of intestinal microbes, or to the influence of products of incomplete breakdown of proteins which are transferred to the blood through the intestine and to which liver failure sometimes assists, we cannot at present answer precisely.

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An Appliance for Preventing Leakage of Gastrostomy and Enterostomy

By
ALEXANDER STRELINGER, M.D.
ELIZABETH, N. J.

THE PRINCIPLE herein described is simple. It uses two well known technical features. One is the soft rubber catheter surrounded at some point near the tip by an inflatable bag, like the Foley catheter; the second is the plain rubber disc with a perforation in its middle; the stem of the catheter can be threaded through it. Foley catheter and mushroom catheter have often been used in an attempt to prevent leakage; but I found no record of their use with a disc in the manner to be outlined here. The Lamson appliance uses the inflatable bag and disc; these two are fixed at an in-

bag and disc is the effective step in successful application for drainage of liquid material or for feeding.

A rubber tube or a catheter should be selected that passes easily but not too loosely through the external stoma of the gastrostomy or of the enterostomy. An inflatable rubber bag is mounted near to the open end of the rubber tube; the Foley catheter is the ready made version of this. The size of the bag varies; in most cases a bag of 20 to 40 cc inflated volume will be practical. If a Foley catheter is used, the whole length of the catheter remains, because shortening the

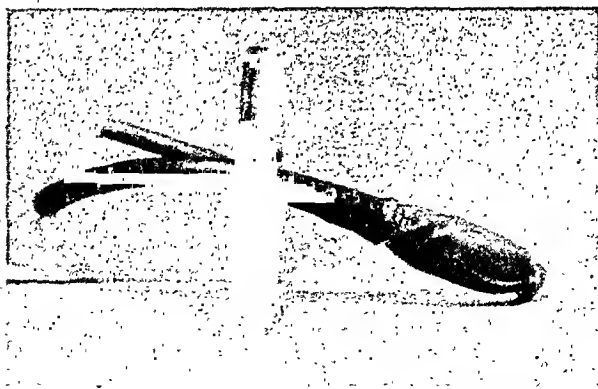


Figure 1. — An appliance for preventing leakage

variable distance; this appliance has no catheter, and is used for occlusion only. Variable distance between

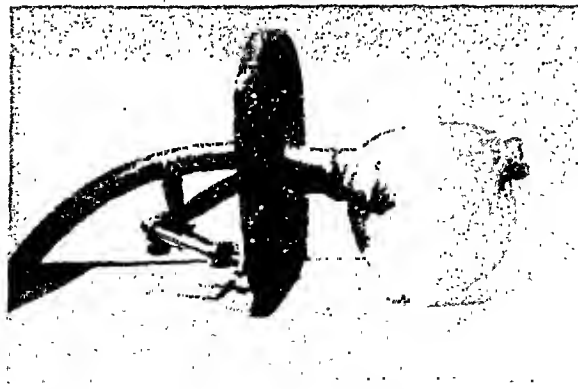


Figure 2. — An appliance for preventing leakage

catheter results in difficulty of retaining the inflating medium of the bag. The appliance can easily be made up in shorter length. Figure 1. and 2. show an appliance made up from short length of rubber tubing.

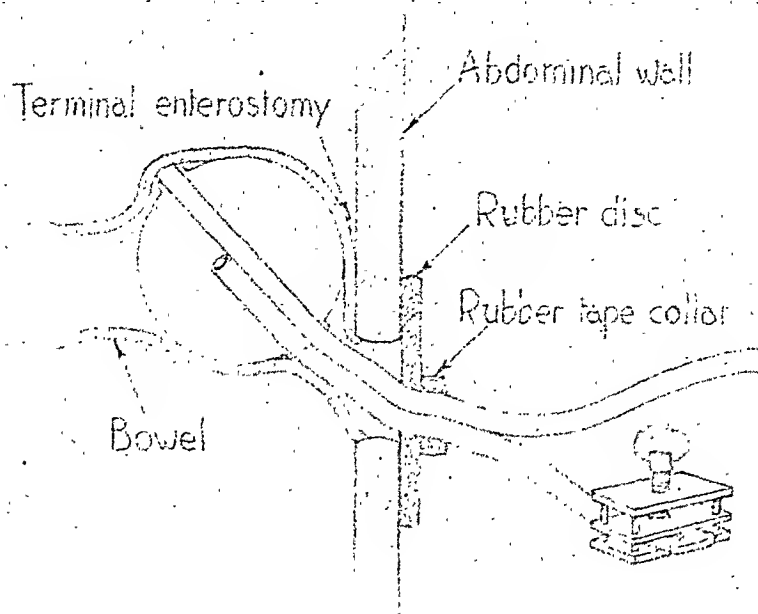


Figure 3. —

Penrose drain, copper tubing sleeves, and dental floss. The heavier tubing passes through the inflatable bag, the lighter inflates the bag, and ends in its lumen. The rubber disc moves freely on the tubes, which are threaded through the hole of the disc. For use the appliance is inserted with the end carrying the bag into the stoma to a distance that will permit inflation of the bag inside of the abdominal wall. The bag is inflated with water, the tube clamped to the bag. The appliance is pulled taut against the inner surface of the abdominal wall, the disc is slid down on the tubes or the catheter stem and pushed snug against the skin. Thus the bag from the inside and the disc from the outside grip the abdominal wall. To retain

them in this position a small length of insulating rubber tape is wound as a collar around the tubes or catheter stem right above the disc. When the appliance is retained in this manner, the tube passing through the bag is used for feeding in patients with gastrostomy. For drainage in patients with enterostomy discharging liquid contents it is used in like manner, but the lumen of the draining tube must be wide. The tube may be connected with a longer tube to a drain bottle; or simply a condom can be tied around its end and used as receptacle for intestinal contents, then changed as required.

There is one prerequisite for the use of this appliance: the stoma itself or a point in the canal passing through

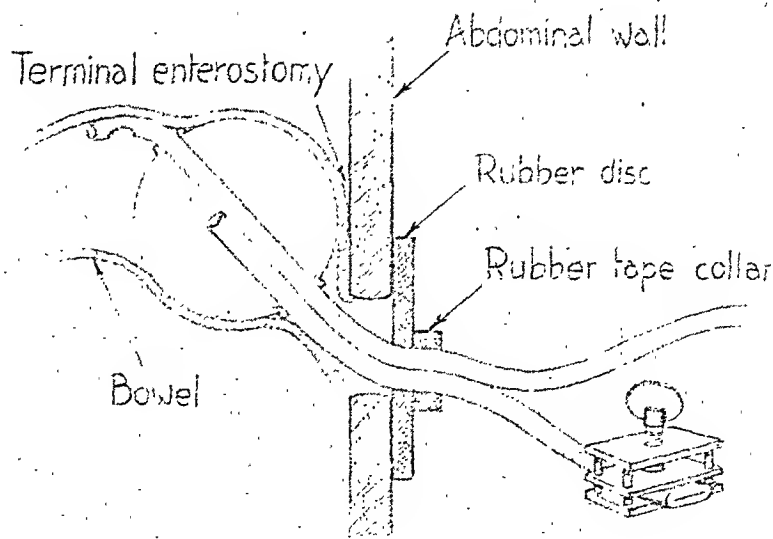


Figure 4. —

the abdominal wall must be narrower than the lumen of the stomach or the bowel within the abdominal cavity. In a recent enterostomy, particularly when the abdominal wall supplicated following the operation, this is not always the case; but it is so with gastrostomies and usually becomes so very shortly with enterostomies. Unless there is such a narrower point, the bag has nothing to rest against.

For draining terminal enterostomies an appliance with the tube-end protruding well beyond the bag is necessary. A short end may become occluded by the bowel wall, like in Figure 3., but the protruding end will not, like in Figure 4.

The essential feature of this principle is obvious.

The inflatable bag provides an efficient plug when the disc on the outside is just at the right distance and prevents slipping of the bag. This is the reason that the appliance can not entirely be made up as a stock item; the surgeon has to fit the appliance first and has to determine just how far the disc must be placed, because this distance varies from case to case. Some patients — after initial fitting — may learn how to remove and clean the appliance, then to reinsert it.

Using proper caliber tubing and material for the bag it may be attempted to occlude any kind of leaking body opening, for instance cystostomy, vesico-vaginal fistula or thoracotomy.

Allergy as a Factor in Headaches

By

JOHN A. TURNBULL, M.D.

BOSTON, MASSACHUSETTS

THE DISCUSSION OF HEADACHES in this presentation will be made with migraine as a point of departure. The various nonmigrainous types will also be considered. They are known under such synonyms as sick headache, migraine, hemicranic, bilious headaches, hemicrania and migraine. These forms of headaches may be a simple or an extremely complex condition, shading at times insensibly into other disease pictures. It is possible only to attempt definition of the more classical types of the affection: there are those related forms which may be bound up with other morbid manifestations.

Typically migraine is a periodically recurring headache, predominantly unilateral in most cases, often prostrating, usually accompanied by nausea or vomiting, or both, lasting from a few hours to several days, and occurring in individuals in apparent good general health. In women the attacks frequently occur in association with the menses. Often the seizures are preceded by visual disturbances, which usually last about fifteen minutes. It is not essential for a patient to present every symptom for the diagnosis to be made. Cases are empirically separated into two groups: those of simple migraine without visual symptoms, and those of ophthalmic migraine with visual symptoms. The attacks may come suddenly without warning or they may be preceded by a period of hours up to a day or two, during which the patient knows that a seizure is brewing, because of a feeling of general discomfort and malaise. There is a general let down in the expression of energy and frequently there is great irritability. The pain is typically limited to one side of the head. It is quite common, nevertheless, for the other side to be involved simultaneously. During the course of the attack the pain may leave one side of the head to become established in the other. By far the most common symptom is nausea. Practically all patients experience it during their attack and usually it is present during the major part of the seizure.

Quite commonly the nausea leads to excessive vomiting, which sometimes relieves the pain transiently. Soon, however, the pain wells up again and the whole cycle may be repeated.

Headache is the most common feature and exhibits a great amount of variability as to location, quality, intensity and duration. In the most classical attacks, the headache begins on the average about fifteen minutes after the appearance of the scotomata, or other sensory phenomena, and frequently begins on one side and may remain so or become bilateral. As a rule, it is frontal, or occupies the vertex, but may involve the temporal regions or the occiput, sometimes as low down as the neck. There is usually pain over the eyes and the eyes are usually painful to pressure, and there is sometimes pain in the malar region. Occasionally there is well marked jaw ache. Throbbing or thumping usually indicates great pressure from within or without.

In some attacks, the head simply feels slightly sore, or heavy or dull or thick "like a block of wood," a frequent expression. Some patients say the pain is agonizing, impossible to describe. Some patients think the head will burst; others that it is being squeezed in a vise. Descriptions of bursting are more common. The pain is all-prevailing, gradually mounting to a maximum, then running along continuously without any break, with at all times a sudden accession. The severity of the pain may be conditioned by a number of factors. Movement uniformly increases it, bending over becomes impossible, noises of various kinds often aggravate the pain tremendously and cause certain patients marked distress.

Migraine may be preceded by a sense of heaviness, with yawning, dizziness, or depression, motor twittings, even sharp spasms, closure of eyelids, sensory phenomena, chiefly paresthesia, occasionally anesthesia, affecting the eyes or other sensory organs, ringing in the ears, blowing, whistling or a sense of taste, smell or of touch.

Symptomatic migraine implies that the symptoms

represent actual organic disease, in which the underlying cause may be physical lesions. The most frequent are brain tumors, especially tumors of the pituitary gland or neoplasms in the ventricular system.

The organs, which have been declared at fault, have been the vasomotor centers, the sympathetic, the gastrointestinal canal, excretory and ductless glands, organs of generation, male and female, the various organs of sense, the eyes, ears, nose and tongue. Alterations in the secretory functions are frequently observed, early or late in the attacks, as vomiting of frothy mucus, sweating, coryza, and urinary secretions.

Brickner (1): "There are four approaches which deserve special emphasis; those of allergy, gallbladder, abnormality and endocrine dysfunction and psychologic. The vomiting which so often accompanies an attack, and which sometimes relieves it, thus naturally led investigators to the abdomen as a source of information. In the same manner it has led to the term 'bilious attack', a description often used by patients. Most of the opinions of the gallbladder phase of migraine depends on the presence of the abdominal symptoms."

McClure and Huntsinger (2) found roentgenologic evidence of gallbladder abnormality in a large proportion of their patients, and of functional disturbances of the liver. Hunt (3) found evidence of gallbladder and liver disturbances. He concluded that "local gallbladder disease or liver dysfunction is not a cause of migraine, but may occur as a result of repeated migraine attacks". Those who have given the most attention to the hepatic origin of migraine state that cholecystectomy is of no assistance.

ENDOCRINE THEORY

It is very frequent for the whole condition to have the onset with the menses. Attacks very commonly occur in association with the menstrual period and it is frequent for them to disappear during pregnancy and lactation and also at the time of menopause, although migraine may occur during or after the menopause.

The term psychogenic headache is frequently applied because of the vague manner in which the patient usually describes the pain. A definite statement about the actual characteristics of the headache is difficult to obtain, to which they exhibit no definite characteristics at all except agony. The type of pain is hard for the patient to describe or a number of different types are specified in which there is a cephalic pressure, or they state that it occurs in every part of the head. Turnbull (4) in: "The Tired, Weak, Exhausted, Depressed Patient" states: "Theirs are not imaginary symptoms. They are not just neurasthenic, hypochondriac, or neurotic cases. In these cases headache is a common complaint, with dull pressure, tightness, feeling as if the head would burst." By avoiding foods to which they were sensitive, these patients were relieved of their headaches.

The allergy theory regarding headache is the predominating one. The other organs or systems, which are disturbed, are upset by allergic reactions in these

organs. Turnbull (5) "These allergic reactions can occur in the gastro-intestinal tract, gallbladder, liver, eyes, ears, nose, sinuses, respiratory, liver, glandular, and in fact, in any part of the body. It is this allergic disturbance that has caused some to consider these organ disturbances as the original cause of the headaches."

Headache is heritage of the rich and poor, the great and the small alike. It has numbered among its sufferers many of the master minds. Hereditary influences are those carried by germ and sperm cells from generation to generation, but other influences may arise and act at an early age, or be delayed until later life. Turnbull states (5) "and manifest itself in headaches or other related allergic conditions. The chief cause seems to be an hereditary tendency to disease. With these individuals the stress and strain during life acts on the individual organism and its constituent cells, thus causing dysfunction in that organ or organs, and in case of headache or other allergic conditions, affects the vasomotor system."

Gray's Anatomy states: "The pia mater is a vascular membrane and derives its blood from the internal carotid and vertebral arteries. It consists of a minute plexus of blood vessels, held together by an extremely fine areolar tissue. It invests the entire surface of the brain, dipping down between the convolutions and lamina, and is prolonged into the interior, forming the velum interpositum and choroid plexus of the fourth ventricle. The lateral ventricles are serous cavities. They are lined by a thin diaphanous lining membrane, the ependyme, covered by nucleated epithelium, with cells scattered here and there in patches. It is moistened by a serous fluid, which is sometimes, even in health, secreted in considerable quantity.

"There is free communication between the ventricles and spinal fluid. To the vasomotor centre is delegated the function of maintaining an adequate blood supply to these vital centres and to the brain in general. If this regulating mechanism is disturbed various results may follow."

It is generally accepted from the work of Dandy (6) that following injection of air into cerebral ventricles, the greater part of the fluid is formed by the choroidal plexuses of the lateral, third, fourth, ventricles. There is a slow movement of the fluid from the lateral ventricle to the third ventricle through the foramen of Monro, thence via aqueduct of Sylvius, to the fourth ventricle; from the fourth ventricle the fluid escapes into the subarachnoid space through the foramen of Luschka, to be finally absorbed in the venous circulation through the arachnoidal villa of the large venous sinuses. The two theories in respect to the method of formation of the fluid are: Mestrezal: The fluid is formed from the blood in the capillaries, of the choroid plexus by dialysis or ultrafiltration. Smith (8): the fluid is secreted by the plexus.

The occasional causing of a passive or active hyperaemia of the brain leads to a hyperaemia of the choroid plexus. This causes a more or less complete plugging of the foramen of Monro with the production of an increase of pressure in one or more ven-

tricles. The increased pressure on the vessels causes more distention and more pressure on the walls of the ventricles, a vicious cycle is established, and the migraine mounts to its height until the pressure is relieved, either by spontaneous reduction or by the sudden let down in tension, due to shock reaction, such as occurs in the act of vomiting, or from use of various vasodilators.

Kennedy (9) stated that other conceptions which have possible validity are those of a process similar to that of angioneurotic edema.

CASE REPORTS

Case 1: Male, age 46. Dentist. Migraine headaches twenty years, pain, excruciating, coming on suddenly, while at his professional work, beginning on left side, later extending to right, accompanied with zigzag visual disturbances, incapacitate him from work, pain excruciating character, reaching its height in forty-eight hours, continuing with this severity for thirty hours, then gradually subsiding next twenty-four hours, these attacks occurring every four to six weeks. Cutaneous test made, diet arranged by avoiding foods to which sensitive, had complete relief from migraine.

Case 2: Female, age 34 years. Consulted me September 15, 1943. Headaches since four years of age continuously, never free of them, worse during summer 1943. Wakes up with headache every morning, temporal, occipital, vertex, both sides, vomiting with the severe attacks, waves of nausea every day, even when not vomiting. Dizziness, head feels heavy, wobbly, large amounts of gas, greater sometimes than others, by avoiding foods to which allergic, free from headaches, nausea, vomiting, gas.

Case 3: Female, age 35. First consultation March 21, 1915, for frequent colds, sneezing, watery nasal discharge for eighteen months, worse during June, July, August. Had a bad cold March 1917. Cough from December 1916 to August 1917. This patient was tested for foods, pollens, animal hairs. With this sneezing, watery nasal discharge which was worse during June, July, August, one would expect to find the pollens the cause of the disturbances during these months, but no reaction was obtained to pollen, which prevailed during this time. Reactions were obtained to fish, which patient ate during those months. She was also sensitive to other foods. By avoiding foods to which sensitive, she was completely free of all symptoms.

Same patient consulted me March 26, 1922. As she had no return to the upper respiratory symptoms in the latter part of 1919, she began to eat miscellaneous foods, disregarding the diet, which had completely relieved all the symptoms at time of consultation, 1918. Soon other symptoms occurred as headaches, which she described as "big head", aching all over the head, mental confusion, abdominal distention, gas, noises in ears, as roaring, sizzling, pains all over the body, from head to toes. On account of the abdominal distress distention, gastro-intestinal symptoms, she was advised to have her gallbladder and appendix removed, which operation was performed March 1920. After these operations the patient's condition grew rapidly worse, with increasing pains in head, depression, confusion, greater gastro-intestinal distress and distention. Talking with this patient caused much mental confusion, so that the patient was unable to answer questions. Since January 19, 1922, she has a tendency to fall either to the right or left. This condition came on suddenly, and on standing with feet together, eyes closed, the patient would sway in a wide angle. It was necessary for someone to be near to keep her from falling. With eyes closed she was unable to touch the tip of her nose with her fingers. Vertigo was very marked and occurred several times a day. In getting into bed, and a feeling as though falling, but this disappeared after being in bed a while. The vertigo would start upon getting out of bed or from rising from a sitting position. Sept., 1921, was nauseated for 7 weeks, vomiting mucus and bile every morning. Aug. 19, 1921, patient had eaten oysters, which was followed

in eight hours by marked swelling of face, eyelids and aching all over the body. This patient had consulted numerous excellent physicians and a neurologist, without any relief. There were increases of all reflexes. By avoiding the foods to which she was allergic, in ten days the abdominal distress and distention were relieved and then began a gradual clearing up of all the other symptoms, nausea and vomiting. She became free of headaches, of pains, and lassitude and mental depression suddenly vanished. Now she could stand with feet together, eyes closed, without swaying, and with eyes closed could easily touch tip of her nose. But should the patient consume any of the foods to which sensitive, the symptoms would indubitably recur. Besides being sensitive to foods, this patient was sensitive to tobacco and tobacco smoke, also very sensitive to cold, especially if she should become very warm or perspiring freely. This patient frequently remarked that she was a proving plant for my test.

This patient was able to resume her professional work as a nurse, and continued until February, 1937, at which time she was exposed to cold, when the heating apparatus in house she was living broke down. Following this, she had a return of the "big head" and other symptoms. Through the influence of relatives, who insisted that she should consult a neurologist, twenty-four hours after this consultation, she became unconscious, was removed to hospital, and operated on. The brain surgeon found an obstruction to the flow of the cerebro spinal fluid, due to a blocking, from edema of the ependyme of lateral ventricle, thus obstructing the flow from the lateral ventricle to the third ventricle through the foramen of Munro, thence via aqueduct of Sylvius, to the fourth ventricle. As patient did not regain consciousness, second operation was made, trying to open the foramina, but was unsuccessful, and the patient died four days later.

In this case, at the first consultation, we had disturbances of the respiratory tract, as shown by sneezing, watery nasal discharge, coughing, which symptoms were relieved by avoiding the allergenic foods. At the second consultation, March, 1922, the patient exhibited symptoms of headache, disturbances of the cerebral, nervous, gastro-intestinal, aural systems, thus showing a syndrome of different systems affected from that of the first consultation four years previously. Here we have a change in the systems affected, and also change in susceptibility to foods. But the mechanism of the systems affected in these consultations bears a striking similarity, in that at first consultation we have vasomotor rhinitis, watery nasal, edema of nasal mucosa, with blocking of the nares, while at second consultation, with the symptoms of headache, as patient described "big head", motor, sensory disturbances, there is no doubt in my opinion, that the symptoms present at time of this visit, were a result of vasomotor dysfunction of the choroid plexus, causing serous secretion producing edema of the lining membrane (ependyme), thus closing the foramen Munro, thus preventing the normal circulation of the cerebro spinal fluid, with the retention of increased fluid, thus retained in the ventricles, causing great pressure in the ventricles.

I do not wish to give the impression that all headaches or migraines are produced in this way, but I am of the opinion that a vaso dilation of the cerebral vessels throughout the brain substance, also are cause of headaches, and other sensory disturbances.

Inhalation of tobacco smoke and other inhalants can produce headaches by their absorption through the nasal, pharyngeal respiratory tract, and eyes.

Case 4: Female, single, age 36. Consulted me Aug. 6, 1931. Migraine headaches all her life, which begins with blur, and zigzag visual disturbances, followed by nausea, pain beginning in the eyeballs, and radiating to temples, then vertex, sometimes starting in the occiput region. These severe attacks come twice a month with no particular relation to menstrual periods. Severe headaches last 5-6 days; never completely free of headaches. Menses began

at 16 years of age, during the first six months, very irregular, then 28-day interval. Pain begins twenty-four hours previous to flow, severe pain for two days at start of flow. Pain so severe as to incapacitate the patient; confined to bed. These periods last from three to five days, flow has been scanty until the last year. Had urticaria in April, 1930. Tired every morning and tired easily for last ten years. Mother has headaches and arthritis. Cutaneous tests made, instructed to avoid foods to which sensitive. Oct. 17, 1931, patient reports no headache, no pain or disturbances with menstrual periods. Not tired.

Case 5: Female, married, age 53. Consulted me March 25, 1946. Headaches 10 years, all over the head, worse left side, and occipital region, usually starts in the morning, last all day, will be all right next day. These attacks occur about twice a week. Had bilious headache from young girl until 33 years of age. Dizziness at times. Whistling noise both ears, noticed more when she gets into bed. Last four months, much sneezing, eyes water freely, nasal watery discharge, cough, raising some mucus all time. Blood pressure from 180 to 200 systolic for 20 years. Considerable gas all time, worse after meals. By avoiding foods to which sensitive had complete relief of headaches, gas, cough, mucus, blood pressure, systolic 140, diastolic 80.

Case 6: Female, age 54, married. Consulted me January 26, 1926. Headaches since ten years of age, which have steadily increased in severity and frequency. Headaches continuous, and so severe as to confine patient to bed three to four days out of every week. The severe attacks of headaches were accompanied by acute epigastric pain which required morphine hypodermically, and she felt all used up for three to four days after these severe attacks, did not feel well more than three days out of every month. Had a general miserable feeling and a confused mental condition, which seemed to have rapidly increased in the last six months. Much sneezing, frequently fifty times in one session. Tired and exhausted all time, and very forgetful. Cutaneous test made. Diet arranged accordingly, by avoiding the foods to which she was sensitive. In four weeks there was complete relief of headaches and all other symptoms.

Case 7: Female, age 42, married. Headaches, all over the head, dull annoying pain. Headaches started five years ago, two to three days out of every week, dizziness frequently. In last two years had three very severe dizzy spells, staggered in walking, had to hold on fence to get into the house. These severe forms last about a week. With the extreme dizzy spells when going to bed at night, feels as if whole room was going around. Has very bad dreams, "regular nightmare." Has severe pains in stomach at intervals. Much sneezing in mornings. Sleeps without any night or bed clothing, so hot that she has to get up three to four times each night to let bed cool off before she can get in bed again. By avoiding the foods to which she was allergic, in two weeks there was complete relief of headaches and all other symptoms. After relief from her headaches, pains, she slept with night clothing on, over her she used sheet, blanket, and comfort.

Case 8: Male, age 57 years. Headaches, for twenty years, two every month lasting from three to five days, sharp shooting pains, starting on the right side, after twenty-four hours then begin off left side, zigzag streaked vision at onset of these headaches. Always has a cough. Eczema of scalp for forty-five years. "Nervous breakdown" 1913. By avoiding foods to which allergic, had complete relief from headache, cough, and eczema completely cleared.

Case 9: Female, age 52, married. Headache, 10 years. Frontal, orbital, severe, sharp pains both eyes. These symptoms are continuous, with acute exacerbations about twice a month, with vertex effervescence sensation. Has sneezing, watery nasal discharge, much gas throughout the abdomen, worse after meals, during the night, nausea, burning sensation in stomach. Ringing in ears, tired for ten years. By avoiding foods to which allergic had complete relief from head and all other symptoms.

Case 10: Female, age 26. Consulted this office Sept. 30, 1924. Headaches, severe sharp pains over whole head,

visual red streaks, with zigzag forms, pain over both eyes, dizzy spells, at times a staggering walk. Feeling at times as if chasing herself. Tired easily. Cutaneous test made, by avoiding foods which gave reactions, was completely relieved of headache and other symptoms.

Case 11: Male, physician, 1922. Following extraction of a tooth, which broke in many pieces, patient developed pulmonary abscess, left lung, just back of the aorta, and vicinity of pulmonary vessels. Patient coughed up eight ounces of mucus and pus each day and had elevated temperature for two years, was bronchoscoped fifty-three times. Following thirty-fourth bronchoscope, developed acute appendicitis, was operated upon ten hours after onset of symptoms. Following this, long illness developed, headaches and blurred vision. Headaches were dull in character, with a feeling of pressure or distention, varying over different parts of the head, with feeling that something serious was going to occur. As a boy, had frequent so-called "bilious spells," frequently jaundice, blocking of nasal passages, sneezing, watery nasal discharge.

COMMENT

I have selected these eleven cases from my files in order to show different phases of headaches, and other associated systemic conditions, either preceding or accompanying these headaches. Of these eleven cases, seven were females, four males. Age varies from thirty-six to fifty-seven years at time of consultation. There were two thirty-six; one forty-two; one forty-three; one forty-five; five between fifty-two and fifty-seven years of age.

Number of years suffered with headaches: 20, 50, 2, 30, 10, 44, 5, 20, 10 years and one, six months.

Frequency of headaches: Every 4 — 6 weeks. Continuous, with severe acute every 2 weeks. Continuous big head. Severe attacks every 2 weeks. 2 headaches each week. Continuous, severe 3 to 4 days each week. Severe acute attacks lasting 7 days. Every month lasting 3 to 5 days. Continuous, acute attacks, two each month. Continuous 6 months.

Part of head affected: One with pain starting on right side extending to left. One "big head" all over. One frontal, orbital, effervescing sensation vertex, with shooting pains all over. One starting temporal, extending to vertex, then occiput. One starting in occiput, vertex, then temporal. One all over head, worse on left side. Five all over head.

As to character of pains: One excruciation from onset. One dull aching, then excruciating. One shooting pains. One dull aching, pressure feeling. Five dull aching.

Visual disturbances: Three, pain both eyes, one with pressure feeling. Four, zigzag, red streaks. Three had vertigo, 4 noises in ears as ringing. 6 sneezing, 5 watery nasal discharge. Two cough, 4 dizziness, 4 nausea, 2 vomiting, 3 acute pains in stomach, 4 mentally confused, 2 tired all time, 1 eczema.

Two bilious attacks years preceding headaches. One jaundice as child, one sleeping without night or bed clothing, bed gets so hot had to get up 3 to 4 times each night allow bed to cool.

One case dysmenorrhoea. In all these cases there is a great variance, as to age of onset, duration, parts of head affected, character of pains with other systemic disturbances. In all cases there was complete relief from headaches and other symptoms.

It is interesting to note that five of these cases had sneezing and watery nasal discharge. With this point in view, I consider it important to review the history of Case 3 from an allergic, physiological and pathological angle.

In 1918, Case 3 consulted me for sneezing, watery nasal discharge. There was edema of the nasal mucosa with a watery secretion over the mucous membrane, both nares. These symptoms were completely relieved by avoiding foods to which she was sensitive, and remained free until latter part of 1919, when she began eating foods to which she was sensitive in previous test. This was soon followed by, as patient expressed it, "big head," nausea, vomiting, gastro-intestinal mental confusion, pains all over body, vertigo, cerebral and motor disturbances. On account of the gastro-intestinal disturbances, she was advised to have cholecystectomy and appendectomy. Following these operations, all symptoms grew rapidly worse. Patient consulted me March, 1922. Cutaneous test made by avoiding foods to which sensitive. There was complete relief from all symptoms. She was able to resume her work as a nurse, and continued until February, 1937, when heating plant in home she was working broke down. She was chilled, and I stated previously in this case she was sensitive to tobacco, tobacco smoke and cold. Any of these could cause her headache. Following this chilling, she developed her "big head". Relatives persuaded her to consult brain surgeon, she was sent home, and in twenty-four hours became unconscious, was removed to hospital and operated on. Surgeon found an obstruction to the flow of the cerebro spinal fluid, due to blocking from edema of the ependyme of the lateral ventricle, obstructing the flow from the lateral ventricle to third through the foramina of Monro, then via the aqueduct of Sylvius to the fourth ventricle. This retention of fluid in ventricles causes distention, with pressure on ventricle walls therefore pressure on cerebral cells.

Mestrezello (10) states: The fluid is formed from the blood in the capillaries of the chroid plexus. In headache, as in Case 3, there are the changes taking place in the ventricles of the cerebrum, that occurs in the mucosa of nasal passages and accessory sinuses, resulting in pain in frontal and antra as result of the edema and pressure.

It is my opinion that in allergy we have a vasodilatation. At this time there is filtration of serum through the dilated blood vessels into the surrounding tissues, and in cases of headaches, this can occur in any of the blood vessels supplying the brain.

Occasionally, I see patients who instead of a vasodilatation, have vasospasm.

CONCLUSIONS

1. Although sometimes symptoms described in headache may seem vague, these patients suffer real pain.
2. Patient may have other systemic disturbances occurring at the same time. They are not the cause of headache.
3. These other systemic disturbances, although not cause of headache, through their dysfunction may increase the headache.
4. These other dysfunctions are caused by the same allergies that produce the headache, and the cerebral changes can increase the dysfunction of the other organs affected.
5. The symptoms referred from other organs clear up at same time as headaches.
6. Many of the headache patients present allergic symptoms in early life or some time before the onset of headaches.
7. Allergy is an important factor in headaches. I find that 93 per cent of my cases are relieved of their headaches by avoiding foods to which they are sensitive.

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Carcinoma of the Colon Secondary to Chronic Ulcerative Colitis *

By
THOMAS M. JOHNSON, M.D.

and
THOMAS G. ORR, M.D.
KANSAS CITY, KANSAS

IN RECENT years increasing interest is being manifested in carcinoma as a complication of ulcerative colitis. There is some difference of opinion concerning the role of polypi and pseudopolypi in the development of carcinoma in patients with chronic ulcerative colitis. A review of the literature reveals the somewhat controversial status of the subject.

In 1927 Yeomans (15) reported 7 cases to demonstrate his concept of the precancerous nature of polyps of the colon. One of these cases was a woman with chronic ulcerative colitis who developed rectal carcinoma. He had previously removed several benign polyps from her colon. It was his opinion that, "Both clinically and by histologic study of the specimens, the transition from simple inflammatory hyperplasia to tumors pathologically cancerous can be traced through the stages of inflammation, gland cell hypertrophy and hyperplasia, and adenoma to definite adenocarcinoma. It is a logical inference that continuance of the irritative factors that induce the adenomas stimulates epithelial hyperplasia until it breaks through normal bounds and becomes malignant." In 1928 Bergen (1) concluded that, "In view of the various reports in the literature, the frequency with which polyposis has occurred in the series of cases of chronic ulcerative colitis at the Mayo Clinic and the simultaneous occurrence of polyps and carcinoma in the diseased colon, the following hypothesis is offered: the sequence of events in some cases of malignant disease of the colon is chronic ulcerative colitis, multiple polyposis and malignant disease." Since 1928 Bergen and Sauer (2), Rankin (11), Jackman, Bergen and Helmholz (8), and Cattell (3,4) have subscribed to the thesis as originally stated by Yeomans and Bergen. In 1943 David (6) stated that, "Prolonged ulcerative colitis, where inflammatory mucous polyps are often seen, is complicated by carcinoma in about 5 per cent of the cases." In 1944 Cattell expressed the opinion that, "For a number of years our observation indicated that malignancy was a rare development on the basis of chronic ulcerative colitis. However, in the last two years we have observed 8 patients with carcinoma arising in ulcerative colitis, and previous to this period, 3 additional patients had been seen. At the present we believe that malignancy, while somewhat rare, is most frequent in patients who have had ulcerative colitis for over 5 years, and in those who have had symptoms for a long time, an increasing incidence of carcinoma has been noted." In 1946 Cattell further stated that, "Ulcerative colitis

predisposes to malignant disease of the colon by the very nature of repeated infection followed by attempts at healing with production of polyps, pseudopolyps, scar tissue, and often malignant growth."

In opposition to the views expressed above, Ewing in 1934 made the observation that, "It is somewhat remarkable that carcinoma rarely develops in chronic ulcerative colitis or proctitis." In 1939 Swinton and Warren, (14), after a study of an extensive material concluded that, "From a microscopic study of a large series of intestines from patients with chronic ulcerative colitis, both specimens removed surgically at varying lengths of time after the onset of the disease, and specimens obtained at autopsy, we believe that chronic ulcerative colitis is not a factor predisposing to the development of polyps. In our patients with ulcerative colitis, following healing of the acute ulcerative process, we have known these pseudopolypoid tumors to regress and disappear. We have never observed the regression or disappearance of true polyps of the large bowel except in rare instances in which the polyp has broken away from its pedicle. This suggests that the pseudopolypoid tumors resulting from known irritation and infection have different fundamental growth characteristics than the discrete and multiple polyps which are not the result of any known infectious process. We have never observed the polypoid changes seen in ulcerative colitis progress to a malignant stage."

Lynn (9) in an excellent review of the literature on this subject in 1945, recorded 98 cases of carcinoma of the colon arising in patients with chronic ulcerative colitis. Since that time 13 additional cases have been reported, (4, 5, 10, 12) and 2 have been seen at the University of Kansas Medical Center, making a total of 113 cases.

The incidence of carcinoma arising in chronic ulcerative colitis in different reports reviewed by Lynn varies from 1.9 to 6.3 per cent, the proportion being much higher in children. In 1940 Jackman, Bergen, and Helmholz (8) studied a group of 95 children under 16 years of age suffering from chronic ulcerative colitis. Six of these children, or 6.3 per cent, developed carcinoma of the colon in later years. The general incidence of this complication is probably about 2.5 per cent.

In 40 instances in which there is a record, the ages of the patients ranged from 18 to 69 years at the time the carcinoma was discovered, with an average age of 40.2 years. The average age at which carcinoma of the colon develops without ulcerative colitis is 53 years.

The duration of the ulcerative colitis prior to the development of carcinoma is recorded in the literature in 38 cases, and varies from only 3 months to

* From the Department of Surgery, University of Kansas, Kansas City, Kansas.

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36 years. The average duration of the colitis has been given by Cattell as 9 years.

The segmental location of carcinoma associated with ulcerative colitis follows rather closely the segmental location of cancer of the colon in general.

In 7 cases of ulcerative colitis found in the literature, and in one of our cases, multiple carcinomas of the colon were found.

At the University of Kansas Medical Center, during the 16 year period between 1930 and 1946, the diagnosis of chronic ulcerative colitis was made in 164 patients. Of this group we know of 2 patients who subsequently developed carcinoma of the colon. The case reports are here recorded.

CASE 1.

A 43 year old white man was first admitted to the Hospital in October, 1942. For 14 years he had had frequent attacks of diarrhea with blood and mucus in the stools. Two years before he had developed a generalized exfoliative dermatitis. X-ray studies demonstrated a chronic ulcerative colitis involving the distal third of the transverse colon, descending colon, sigmoid, and rectum. Sigmoidoscopic examination revealed patchy ulceration of the rectum and a rectal stricture. During the hospital stay agglutination tests and stool examinations for parasites and amoebae were negative.

An ileostomy was done by dividing the terminal ileum and bringing both ends out through the abdominal wall. The patient was dismissed on the 17th postoperative day with instructions to irrigate the distal end of the ileostomy with warm water daily. With this treatment he improved, and gained 10 pounds, up to his normal weight of 145 pounds. The ileostomy functioned well.

About three months before the second admission in October, 1945, the patient noticed increasing pain, steady and dull in character, and a mucopurulent discharge in the distal limb of the ileostomy. Abdominal examination revealed a tender, hard mass in the right lower quadrant. At operation a large, hard mass was found involving the cecum and extending into the mesentery of the distal limb of the ileostomy. There were two large tumor nodules in the liver. Biopsy of an enlarged mesenteric node was reported adenocarcinoma. This patient returned home and died five months later in March, 1946. An autopsy was not done.

CASE II

A 32 year old white male was first admitted to the University of Kansas Medical Center in July, 1946, with the complaint of "ulcerative colitis" of sixteen years duration. A barium enema confirmed the diagnosis of ulcerative colitis which existed throughout the entire colon and in addition showed a proliferative process in the transverse colon near the hepatic flexure. By sigmoidoscopy patchy areas of ulceration were seen in the rectum and sigmoid, more marked at the recto-sigmoid. Shortly after admission

he began to have very profuse rectal bleeding and passed large quantities of dark blood and clots. The continued bleeding resulted in shock. After repeated transfusions his condition improved, and the abdomen was explored. A large mass was found in the transverse colon near the hepatic flexure. This mass was mobilized and brought out as in an obstructive resection. Abdominal exploration revealed another questionable mass in the sigmoid colon. The pathologist's report of the excised mass was adenocarcinoma. The postoperative course was satisfactory except for a troublesome excretion of the skin about the colostomy. He was dismissed in September, 1946, with instructions to return for colectomy after his general condition improved.

He was re-admitted in February, 1947, after having gained 30 pounds in weight. After preparation with sulfasuxidine, the colon, with about 15 cm. of the terminal ileum, was removed down to the lower sigmoid. A permanent ileostomy was done. The pathologist reported a mucoid adenocarcinoma of the sigmoid colon and an early malignant polyp of the cecum. There were no metastases found at the operation and none were reported by the pathologist. The patient was dismissed on the 22nd postoperative day with a well functioning ileostomy.

SUMMARY

In Case I there was no evidence of carcinoma in the cecum and ascending colon at the time of the first hospitalization and ileostomy. Subsequent developments illustrate the necessity of frequent X-ray studies in such cases. When warning symptoms appear, such as an increase in pain, change from tenesmus to steady dull pain, increased bleeding or massive hemorrhage, obstruction, cachexia or marked anemia, malignancy should be suspected.

In Case II attention was called to the malignant change by massive hemorrhages and X-ray evidence of a proliferative lesion in the transverse colon. The second adenocarcinoma developing in the sigmoid, and the malignant polyp in the cecum found at the time of colectomy, demonstrate the value of colectomy. This case also demonstrates the importance of repeated proctoscopic and X-ray studies of patients having chronic ulcerative colitis. If multiple polyps are found, serious consideration should be given to immediate colectomy.

The ages of the two patients reported were 32 and 43 years. These ages are in accord with recorded evidence that carcinoma develops earlier in patients with chronic ulcerative colitis than in patients without colitis. The presence of three separate carcinomas in the second case, one of which was known to be a malignant polyp, suggests that the carcinoma in this case developed from polyps rather than pseudopolyps.

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The Importance of Occult Blood in the Stool *

By

W. D. PAUL, M.D.

and

H. E. HAMILTON, M.D.

IOWA CITY, IOWA

THE PHYSICAL EXAMINATION of patients having gastro-intestinal disease may reveal little except for the presence of occult blood in stools and/or changes in the rectum which can be found by digital examination. The accurate diagnosis of disease of the gastro-intestinal tract requires laboratory aids, many of which are expensive and complicated. While digital examination of the rectum is considered an essential part of the physical examination by many physicians, the examination of the stools for occult blood is too often neglected.

Frequently, because this simple procedure is omitted, the presence of a serious disorder in the gastro-intestinal tract is overlooked. It has been pointed out that the diagnosis of disease in Meckel's diverticulum is based upon the findings of occult blood (1). Chesterman states, "In the clinical examination the only positive finding is blood in stools, either as melena or occult blood. Physical examination of the abdomen, sigmoidoscopy and radiological examinations are invariably negative" (2). The diagnosis of peptic ulcer is often difficult even with X-ray examination and it is therefore important to examine the stools for occult blood.

In the study of 110 cases of carcinoma of the large and small bowel, Dahl, Iversen and Nissen found persistent occult blood in 74 cases (67 per cent), intermittent occult blood in 28 cases (25.5 per cent), and no occult blood in 8 cases (7.3 per cent) (3). Though occult blood is usually present in the stools of patients with carcinoma of the stomach, unfortunately its absence does not exclude the disease, for scirrhous carcinoma may not ooze or ulcerate. Also, pancreatic disease reduces the reacting power of the blood considerably by inhibiting peroxidase (4, 5, 6).

Although the dark tarry stool is a significant finding, reference is made to the work of Daniel and Egan under the direction of Ivy (7), who showed that the quantity of blood that must be taken by mouth to produce a tarry stool is 50 to 80 cc. (approximately a half water glass). An occult blood test will show blood when present in quantities as small as one drop per average stool (8). Other work shows quan-

ties up to 200 cc. necessary to produce a tarry stool (9).

The importance of the digital examination cannot be overstressed and it is productive of a great deal of information. The tone of the rectal sphincter, ischio-rectal abscess, masses, strictures, or other abnormalities may be diagnosed by this procedure. Harris has pointed out that "nearly half of the carcinomas of the colon or rectum can be diagnosed by digital examination" (10). The size, consistency, shape and state of tenderness of the prostate and seminal vesicles can easily be determined. In the female the size, consistency, and position of the cervix can be ascertained by palpation through the rectal wall.

It has been our practice to make tests for occult blood following the digital examination. Upon withdrawal of the digit after routine rectal examination, particles of feces which adhere to the gloved finger can be washed off with a few mils of water and a chemical test for occult blood performed (11). A technique that has been employed at the University hospitals is as follows: Following the digital examination, the gloved finger is placed over the top of a three quarter inch test tube containing 5 cc. of water. The tube is shaken so that the adhering stool specimen is washed from the end of the gloved finger and a drop of this solution is placed on a small piece of filter paper. An orthotolidin tablet* is placed on this moistened filter paper and 2 drops of water are permitted to flow over the tablet and down on the filter paper. If occult blood is present, the filter paper about the orthotolidin tablet will turn a blue color of varying intensity within a two-minute period.

Even though there is no visible fecal material adhering to the gloved finger (and this is frequently the situation when the rectum is empty during a digital examination) the material obtained will frequently be sufficient to give a positive reaction if the preceding stool specimen contained occult blood.

Orthotolidin, benzidine, and phenolphthalein tests are commonly used for occult blood. Usually, reagents are required which are difficult to handle, such as glacial acetic acid and fresh hydrogen peroxide. Recently, a tablet has been made using orthotolidin as the reagent (Hematest tablets)*. These tablets are

* From the Department of Internal Medicine, State University of Iowa, Iowa City.

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* Hematest tablets supplied by Ames Company, Inc., Elkhart, Indiana.

stable, do not take up moisture, and can be carried around in the doctor's bag, employed in the patient's home, doctor's office, and laboratory. Although these tablets are extremely sensitive (12) for occult blood, the color intensity reaction and time reaction are important. Occult blood in proportions of 1:20,000 will give a blue color within two minutes.

Andrews and Atchley ran a number of occult blood tests from various parts of a stool specimen, and found the reactions to be uniformly positive or negative throughout the entire specimen (8). Similarly, evidence of one hemorrhage may remain in the bowel as long as two weeks (9, 13, 14).

The following case reports will illustrate the importance of an adequate digital examination of the rectum and the use of a test for occult blood.

CASE I

History: R. A., white male, aged 61, entered the University Hospitals January 9, 1947, with the complaints of upper abdominal pain for two months and weakness for six years.

The patient was perfectly well until ten years ago when he began to have vague pains in the upper abdomen usually noted after meals, not relieved by food or soda, but often relieved following a bowel movement. An appendectomy one year later was followed by complete relief of all his symptoms.

About two months before admission, the patient became more constipated than usual and developed a pain in the upper abdomen. The pain increased when he worried about his constipation and was relieved by a bowel movement. There had been no chills, fever, or sweats. At no time had there been jaundice, dark colored urine, or changes in the normal color of the stool. There had been no nausea or vomiting. In the past few months he had lost about two pounds of weight.

In 1940, the patient had noted for the first time the onset of fatigability and weakness, pain in both hips, a "burning and a hurting" of the tongue, and a sensation of numbness and tingling in his hands. His legs became so weak he could hardly use them. A diagnosis of pernicious anemia was made, and since that time the patient has taken bi-weekly intramuscular injections of 1 cc. of liver extract. At times, the liver injections were given as frequently as every other day and supplemented with heavy doses of oral liver therapy.

In spite of the medication, he continued to have remissions and exacerbations of the anemia; the exacerbations were characterized by periods of weakness and fatigue following the slightest effort to work. In May, 1946, his red blood count was reported to be one million. At no time, to his knowledge, had a rectal or stool examination been performed.

Physical Examination: On admission, the patient was well developed and moderately nourished. The skin was moist and of normal texture. The hair was gray. The head and neck were negative. The tongue was normal in character with no evidence of glossitis or atrophy. There was no evidence of enlargement of the heart, increased activity, or murmurs. The lung findings were normal. The abdomen revealed a well healed lower right rectus scar. There was generalized tenderness on deep palpation over the entire abdomen but more particularly over a palpable spastic colon. No masses were present. The liver and spleen were not demonstrably enlarged. The reflexes were bilaterally equal and the deep and superficial sensations were intact. There were no abnormal neurological signs. The rectal examination revealed a normal prostate, no masses or tenderness, and no evidence of hemorrhoids. Digital examination revealed a strongly positive reaction for occult blood.

Laboratory Examination: The chemical reaction for dextrose, hemoglobin, bile and urobilinogen were negative. The red blood cell count was 3,500,000, the white blood cell count was 5,050, and the hemoglobin, 12 grams. The differential blood count: 56 segmented polys, 37 lymphocytes, 2 eosinophiles, and 5 monocytes. The red blood cells on direct smear were normal in appearance. The reticulocyte count, hematocrit, clot retractility, R. B. C. fragility, platelet count, and bleeding and clotting time were all within normal limits. Numerous stool examinations revealed a strongly positive chemical reaction for occult blood. No parasites were found in the stool by direct or concentration methods. The Van den Bergh test was normal on two occasions. An E. K. G. was normal. Gastric analysis revealed free acid of 80 units after the administration of histamine. X-ray of the gallbladder showed a normal functioning gall bladder without evidence of stones. GI series, colon series, and a motor meal showed no abnormality.

Sigmoidoscopic examination revealed a normal lumen, pliable walls, and rugae present. In the sigmoid were several pin-point hemorrhages. One area 0.5 cm. in diameter was denuded of mucosa and bleeding. At the junction of the sigmoid and rectum, slight granularity was noted. Several small areas of bleeding were noted in the rectum. Most of the rectal mucosa was granular. The colon was essentially normal. No masses or polyps were seen.

As this history was reviewed, it became apparent that the patient had had vague gastro-intestinal complaints for many years, but the outstanding symptomatology was in reference to an anemia. It was unfortunate that a digital examination had not been performed earlier since the presence of occult blood led to the establishing of the diagnosis in this case. It was believed that the recurrent blood loss in this case was due to benign ulcerative colitis.

CASE II

History: W. W., white male, age 64, has been seen repeatedly at the University Hospitals during the past 21 years. During this period of time varied diagnoses had been made. In 1941 he fell and sustained a simple fracture of the vault of the skull. Since then he has been re-examined frequently for a possible post-traumatic epilepsy.

On April 11, 1947 he was referred to the medical outpatient clinic by the neurologist because of a persistent cough. The patient complained of a poor appetite and loss of weight over the preceding year. He had had cough at night for many years. He denied ever having abdominal pain, constipation, diarrhea, blood in the stools, or change in bowel habits. He had always had two bowel movements daily. The rest of the history was irrelevant.

Physical Examination: On present admission, the patient was well developed, well nourished and appeared to be in good health.

Examination of the head, neck, chest, lymph glands, and cardiovascular system was negative. The abdomen was scaphoid in contour; the liver was palpable three centimeters below the costal margin, and no masses or tenderness were demonstrable.

Rectal examination revealed hemorrhoidal tags. The digital examination was negative for tenderness and no masses were encountered. The specimen obtained at this time on the glove tip was strongly positive for occult blood.

Laboratory Studies: The urine was negative for albumin, blood, and sugar. The R. B. C. was 4.3 million; the W. B. C. was 9,150. The blood Kline and Kolmer reactions were negative.

Because of the presence of occult blood in the stool, an x-ray examination was carried out and a sigmoidoscopy was done. The colon series was negative. On sigmoidoscopy the rectal mucosa was normal throughout, except for the presence of a large polypoid tumor approximately 12.5 cm. from the mucocutaneous junction. The

tumor measured 1 x 1.5 cm., had a narrow pedicle and a broad, irregular, and bleeding head. The impression at this time: a polypoid adenocarcinoma of the rectum. A biopsy specimen was removed for microscopic study. The pathological report was an adenocarcinoma of the rectal mucosa.

Treatment: The patient was then admitted to the department of surgery for an abdominoperitoneal resection and no evidence of metastatic lesions was discovered. The patient made an uneventful recovery and was discharged from the hospital.

In this case, even after the diagnosis had been established, no history suggestive of any bowel disorder could be obtained. The diagnosis depended upon the occult blood test which was a part of the complete rectal examination.

CASE III

History: P. H., a white female, aged 22, entered the University Hospitals February 16, 1947, with the complaints of nervousness for many years, stomach distress for one year and weight loss for the past four months.

The patient had been "tired and worn out" since the age of 12. She had always been shy and found it difficult to mix with people, and had no close friends. About two years ago her "nerves," which had always been "bad," became worse with episodes of trembling and pounding of the heart. She was unable to stand people being around because of her nerves and had to leave her job as a clerk in a store. For many years she had been constipated and had used strong laxatives. She had always experienced vague abdominal pains. In addition to these complaints, she noted a gradual loss of appetite about one and a half years ago. At that time, there was also an intermittent left abdominal pain which radiated to the left thigh. About one year ago she developed epigastric distress which was not related to meals. For the past six months the patient complained of "chills and hot flashes." During the past four months the patient lost 18 pounds of weight. There had been no nausea or vomiting until two weeks before admission. All of these complaints seemed to be closely related to her nervousness.

Physical Examination: The essential findings on admission revealed a pale chronically ill young woman who was poorly nourished. The abdomen was tender in the epigastrium and there was marked muscle guarding. No masses were palpable. There was tenderness in the costo-vertebral angles. The rectal examination provided a strongly positive occult blood test. The rest of the physical examination was essentially negative.

Laboratory Studies: The urine analysis was negative for albumin, blood, and sugar. The R. B. C. was 3,650,000. The W. B. C. was 19,969 and the hemoglobin was 7 grams. The gastro-intestinal series revealed a huge ulcer on the

lesser curvature of the stomach showing a meniscus sign. At 4 1/2 hours there was 75 per cent gastric retention. Impression: suggestive malignancy. Gastroscopic examination revealed an extensive ulcerating lesion, the margins of which appeared to be piled up. The ulcer extended from the posterior wall to the anterior wall including the lesser curvature. Impression: carcinoma of the stomach grade II.

Clinical course: Following several transfusions, a laparotomy was performed. At operation, a large mass was found which apparently had its origin in the stomach and had invaded the liver, left kidney, and the tail of the pancreas, and had extended to the vertebral column and about the aorta. It was felt that the neoplasm was inoperable, thus a complete removal was not attempted. The patient was discharged 21 days after admission to the hospital.

When this patient was first seen in the out-patient department her story was considered that of an inadequate personality with a mixed psychoneurosis. It was never possible to date the onset of the symptoms due to the organic lesion. Furthermore, the physical examination was "essentially negative" except for the fact blood was found in the stool following the routine digital examination of the rectum. This positive finding led to the ultimate diagnosis.

COMMENT

Three cases are described somewhat in detail to illustrate the value of a test for occult blood as a part of the physical examination rather than as an occasional laboratory procedure in suspicious cases.

Because of its simplicity, the orthotolidin tablet method for detecting occult blood may be applied routinely. No stool specimen, in the ordinary sense, is required — the washings from the gloved examining finger are adequate to detect even traces of occult blood.

SUMMARY AND CONCLUSIONS

1. The digital examination of the rectum and the test of a fecal specimen for occult blood should be a routine part of each physical examination.

2. It is believed that an earlier recognition of a suspected or unsuspected disease process in the gastro-intestinal tract will be made if this simple and expedient procedure is carried out.

3. The procedure for a rapid and simple tablet test for the detection of occult blood in the stool is discussed.

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Editorial

SPECIAL DIETS

SPECIAL DIETS are sometimes used unnecessarily. An internist told me that on taking over the practice of a physician, he inherited many patients whose chief ailment was malnutrition. These scrawny, unhappy persons had been placed on special diets, usually without reason. The office contained an indexed system of diet sheets, one for almost any conceivable diagnosis. His predecessor was a tall, gaunt man of ascetic temperament and the diet lists reflected his abstemiousness — insufficient calories, protein of poor biological character and puzzling food combinations whose *rationale* was far from obvious. The patients tended to remain on the special diets indefinitely unless told to stop them. The new internist achieved "miraculous" results by merely permitting these individuals something to eat.

The physician, in matters of diet should be influenced first by the body of scientific knowledge known as Nutrition, and second, by the *food knowledge of the race*. It is both asinine and wicked to restrict a patient's diet without abundant reason. Our inherited diet — *what Americans have always eaten* — is a hundred fold safer than the faddy, ill-balanced menus frequently prescribed even by Doctors of Medicine. It is a professional misdemeanor to recommend special diets without reason, since it harms the patient and betrays an unwarranted trust.

Today there is a perceptible movement away from special diets. Diabetics are being given more carbohydrate. Nephritics are being allowed as much protein as they can take care of. Some persons with mucous colitis do better on a general, than a "smooth" diet, simply because they eat more. Today, acceptability is a primary criterion in constructing a menu. Mental and emotional tranquility is three times as important to the ulcer patient as diet. The fat patient fails to lose weight on a low-calorie diet unless something in his brain is altered, because otherwise he will not follow the diet. So far as vitamins are concerned, the public has taken us too literally, as evidenced by the rising generation of young "giants", particularly from the homes of the affluent. We do not know as yet what the future holds for these products of an advanced pediatrics — these unfortunate children who, because of too much stimulation, have missed childhood.

The nutrition expert is the first to admit that there

are many unexplainable facts in diet. In certain sections of Canada the exclusive winter diet of salt pork, potatoes and maple syrup can boast few vitamins except ascorbic acid, yet here we find men vigorous in their late seventies. In the Himalayas certain men withstand the rigors of sub-zero weather, whose total daily intake consists of a handful of parched corn. The wild dogs of Northern Canada who draw heavily laden sleds for ten hours a day across the frozen wastes customarily receive, as their maximum daily allowance, not more than a cupful of cornmeal cooked with tallow. We see women with true *anorexia nervosa* survive for months and years on diets of 200 calories per day. On the other hand there are gourmets, frequently adipose, living and well at eighty. We see fat men waddling happily along in their seventies with perhaps only a little arthritis and blood-pressure. Such facts, of which many more could be cited, should make us humble in our assumption of dietary knowledge.

I was consulted for a minor ailment by a woman who appeared to be 35 years of age. I was impressed by her beauty, vitality and youth and was dumbfounded to discover that her age was actually 65. As I looked at her she seemed to constitute in herself some sort of miracle, some defiance of the laws of nature. My hunch was that she had probably followed an unusually varied, nutritious and scientific diet — perhaps had stumbled onto such a diet by accident. Believing that I was about to discover a "case celebre" in dietetics, I inquired as to the kinds of food she customarily ate. "My diet is very peculiar" she replied, "for twenty years I have cared for nothing at all except bread and butter and tea and have eaten nothing else at all."

When a special diet is actually needed it should, while serving its special purpose, approximate a "normal diet" as nearly as possible. Furthermore, the patient should be relieved of the special diet as soon as its function has been fulfilled. The evolutionary process by which the race has learned what to eat, constitutes an experiment on a grand scale and deserves our humble respect. Smugness in dietetics betrays a dwarfed and limited viewpoint. Nutritional science is invaluable, but the long life span of man makes him an unsatisfactory experimental animal.

BEAUMONT S. CORNELL, M.D.

Book Review

Diagnosis in Daily Practice. by White and Geschickter (\$15.00) J. B. Lippincott, Philadelphia, Pg. 693.

It is a pleasure to read "Diagnosis in Daily Practice" by White and Geschickter, for it presents a new approach in arranging material. It is really amazing the amount of information this book is able to give through the precise and concise organization of its details.

This book is divided into five parts. The first part is called the diagnostic survey. It discusses pre-symptomatic and clinical diagnosis and then, gives a statistical survey of diseases. The diagnostic survey includes tables on mortality and length of disability of certain major diseases.

In the second part, the diagnostic abnormalities and symptoms in general are discussed. Of special interest, are the drawings showing the site of the different skin diseases. Symptoms like worry, uneasiness, itching, lameness, and backache, are analyzed and the conditions mentioned, where they are found, and what importance they have. The physical findings are discussed in the third chapter. The fourth chapter contains the laboratory methods. The authors emphasize the use of those methods which are simple and easy

to perform in the office. The most important section of the book, the fifth part, deals with the major diseases. They not only cover the purely medical conditions, but also diseases of the skin, gynecological, peripheral, vascular, and neurological diseases, and many others. Some chapters are devoted to psychopathic states and psychoses. Chapter five also contains discussions of the clinical features of the major diseases and tables on their differential diagnosis, setting forth the symptoms and signs to be elicited and the procedure to be taken in arriving at a final diagnosis.

The print is clear and the arrangement of the tables and indexes is very effective, so that the desired information can be found very easily. The index is exhaustive and the cross index is very good. Throughout the book we find beautiful colored photographs of different skin diseases, oral pathology, eye diseases, and other conditions. The 360 black and white illustrations and over 100 tables increase the value of the book. It is of special value to the general practitioner and specialist for looking up information which he has not just at his finger tips. This book can be most highly recommended.

FRANZ J. LUST, M.D.
NEW YORK, N. Y.

Abstracts Of Current Literature

ABSTRACT EDITOR — M. H. F. FRIEDMAN
Jefferson Medical College
1025 Walnut Street
Philadelphia, Pennsylvania

CLINICAL MEDICINE

Stomach

VINSON, PORTER P.: *Diagnosis and treatment of cardiospasm* (Southern Med J., V. 40, p. 387, 1947).

Regurgitation, difficulties in swallowing, epigastric or substernal pain and difficulties in breathing are the chief symptoms of cardiospasm. The cause of cardiospasm is failure of relaxation rather than true spasm of the cardiac musculature. Dilatation and redundancy of the esophagus are complications arising in patients with cardiospasm of long duration. Neurogenic influences are probably involved in most cases.

Cardiospasm should be differentiated by roentgenologic studies from diffuse esophageal spasm, carcinoma of cardia and gastric hiatus herniation. Symptoms are intensified by emotional stress. It occurs more often in men than women and most frequently in the second and third decades. Ulcerations of the esopha-

geal mucosa are present if retention of food and fluids in a dilated esophagus is marked. After an initial drop in weight the weight remains constant; a progressive loss in weight suggests cancer of the esophagus rather than cardiospasm.

Regurgitation of food and esophageal secretions are characteristic of cardiospasm and esophageal diverticuli. Strangulation may occur from material regurgitated during sleep. Cardiospasm of children is usually transitory and passes without special treatment.

The epigastric or high sternal pain may be easily confused with pain of coronary or gall bladder disease: The pain is not always associated with swallowing.

Hydrostatic dilators or esophageal sounds are the best means of instrumental correction. In about three-quarters of the patients permanent relief may be obtained by one or two dilatations. Discomfort from the procedure is minimal and no deaths have been associated with dilating 500 patients.

KAPLAN, H.S. AND RIGLER, L. G.: *Pernicious anemia and susceptibility to gastric neoplasms.* (J. Lab. Clin. Med., V. 32, p. 644, June, 1947).

Evidence presented in the literature is reviewed and considered in the light of present knowledge of the gastric cancer problem. Statistical study of the case records shows that pernicious anemia and gastric cancer develop in the same individuals more often than would be determined by mere chance. Consequently the two diseases have an etiologic relationship. The evidence suggests that this relationship is in the nature of a common factor but its exact nature is not known. Hereditary tendencies, achylorhydria, gastritis and the liver therapy received by the patient have been considered as possible factors.

Benign and malignant epithelial stomach tumors were found in 13.5 per cent of 259 patients with pernicious anemia. This is in very great contrast to the relatively low frequency of tumors in the unselected population. Pernicious anemia patients should therefore be studied for gastric malignancy. Similarly other conditions may be etiologically related to cancer in other systems. Practical selective mass surveys for early detection of cancer would be facilitated by establishing the existence of such relationships.

Bowel

JACKMAN, R. J.: *Diagnostic errors in carcinoma of the large intestine.* (Proc. Staff Meet., Mayo Clinic, Oct. 1, 1947, Vol. 22, No. 20, 447-450).

More than half (54.3 per cent) of all patients with carcinoma in any part of the large intestine in the group studied had lesions which could be palpated by digital examination of the rectum. About a fourth (23 per cent) of the patients in this group had received some form of treatment for disease of the colon or rectum, but not for carcinoma, during the course of their symptoms arising from the unsuspected carcinoma that was within reach of the examining finger.

An additional 16.2 per cent of all the patients who had carcinomas anywhere in the large intestine had lesions which were within reach of the sigmoidoscope. A fourth (25.8 per cent) of this group had received treatment for some condition other than the carcinoma, which had remained undiscovered.

Patients who had carcinomas of the large intestine that were beyond the reach of the examining finger and sigmoidoscope constituted the remaining 29.5 per cent of the total series of 817. Of this group of 817, 28.4 per cent had carcinomas that were diagnosed by roentgen-ray studies of the colon, and 1.1 per cent had lesions that were discovered at abdominal surgical exploration. In this group, during the period of symptoms from carcinoma, only 9.9 per cent of the patients had received treatment directed toward any other condition.

FELSON, B. AND BERNHARD, C. M.: *The roentgenological diagnosis of appendiceal calculi.* (Radiology, August 1947, Vol. 29, No. 2, 178 — 191).

From a series of 100 cases reported in the literature and an additional 10 cases reported here, it is concluded that the occurrence of stones in the appendix is a serious and not infrequent condition. The almost constant presence of acute appendicitis in these cases, with an incidence of perforation of nearly 50 per cent, makes the importance of early diagnosis obvious. We have been able to diagnose this condition from roentgenologic evidence in 9 patients. Seven of these were operated upon and the diagnosis was verified.

Once the diagnosis of appendiceal calculus is made, immediate surgery is indicated. The value of roentgenography in acute abdominal conditions is stressed. It is felt that in every case of laminated calcification in the right lower quadrant the diagnosis of appendiceal stone should be entertained and immediate steps be taken to confirm or disprove it.

ROBBIN, L.: *Congenital megacolon in young infants and children.* (Arch. Pediatrics, Sept. 1947, Vol. 64, No. 9, 459-475).

The author reports two cases of congenital megacolon who responded favorably to syntropan. Both cases required laparotomy, one when first seen with an obstructing fecal mass and the other, for the same reason, during the course of treatment when the parents had discontinued syntropan for 3 months. In both operations obstruction was relieved manually without opening the colon. Marked clinical improvement followed the use of syntropan (so long as it was continued) although X-ray studies indicated very little alteration in the gross pathology of the colon. There is a discussion of the rationale for the use of a parasympathomimetic drug. Sympathectomy has the disadvantage of precluding the consciousness of visceral pain.

UPHAM, R. AND SHOOKHOFF, A. B.: *Anemia due to endameba histolytica.* (Rev. Gastroenterology, Sept. 1947, Vol. 14, No. 9, 613-615).

The authors report a comparatively mild case of anemia which did not respond satisfactorily to iron and liver therapy until a diagnosis was made by finding the endameba histolytica in a stool specimen obtained after Epsom salts. There was no clinical evidence of colitis. The commonest site of the lesions in amebiasis is the cecal region and there may be a parallel in these cases to carcinoma of the colon in which anemia is the only manifestation, since these are usually cancers of the cecum or ascending colon.

ZUCKER, G.: *Amebic Granuloma of the cecum.* (Rev. Gastroenterology, Sept. 1947, Vol. 14, No. 9, 609-613).

Zucker believes that chronic amebiasis is present in

from 5 to 10 percent of persons living in the temperate zone. He is concerned with chronic amebic infestation, particularly the so-called "amebic granuloma" of the cecum which gives the radiological appearances of carcinoma. He describes a case occurring in a former syphilitic, whose presenting symptoms consisted of fever, malaise, anemia, severe diarrhea, bloody stools, a palpable mass in the right iliac fossa and some hepatic enlargement. The X-ray revealed a conical deformity of the cecum. The diagnosis was made by warm stool examination which revealed both the trophozoites and cysts of *endameba histolytica*, although frequent ordinary stool examinations had been negative except for the presence of occult blood. He was dramatically improved by emetine and chiniofon, followed by a course of carbarsone. The diarrhea, malaise and anemia rapidly disappeared, the liver receded and there was considerable restoration of the cecum toward normal as revealed by X-ray. A follow-up could not be done as the patient disappeared.

GRIES, D. F., DIXON, C. F. AND BARGEN, J. A.: *Complete duplication of the large intestine: report of case.* (Proc. Staff. Meet. Mayo Clinic., Vol. 22, p. 141, April 2, 1947).

Duplication of the large bowel has been reported only several times. The present case was a 27 year old woman who in recent months experienced abdominal cramps and found it necessary to take a weekly cathartic. At operation she was found to have a completely duplicated colon. Both colons extended from the ileocecal region to the rectosigmoid. However, only the mesial colon was patent throughout; the lateral colon ended in a blind sac at the sigmoid. Both colons were suspended from the same mesentery. Previously the patient had had two appendices removed. She was also found to have two uteri and only a single kidney. In a two stage operation about 8 to 10 inches of both colon segments were resected and a colostomy established. Later the stoma was closed after first applying clamps to the stoma. In this manner both colons were provided with an opening into the rectum. Intestinal function became normal and no further cramps were experienced.

Pancreas

SHERMAN, H.: *Islet cell tumor of pancreas in a newborn infant (nesidioblastoma).* (Am. J. Dis. Child., July 1947, Vol. 74, 1, 58-79).

In the case reported, twitching involving all extremities, the neck and the face began 24 hours after birth. Convulsions developed. A good response was obtained to the administration of dextrose and epine-

phrine. After making a diagnosis of primary hyperinsulinism, an exploratory laparotomy was done but the surgeon did not resect the pancreas because it *appeared normal*. This was an error because at autopsy a typical islet cell adenoma was found. The tumor was almost microscopic in size, yet the hormone secreted by it was either so great in amount or so potent in its effect as to cause a fatal outcome despite the supportive therapy. The mother had symptoms of fatigue, somnolence and excessive sweating during the latter part of gestation, suggesting a hypoglycemic effect on the mother by the excessive insulin-secretory activity of the fetal pancreatic adenomatous tissue. The nesidioblastoma probably functioned before delivery.

VEGHELYI, P. V.: *Secondary pancreatitis.* (Am. Jour. Dis. Child., July, 1947, Vol. 74, No. 1, 45 - 51).

Secondary pancreatitis is most frequently associated with mumps. The symptoms may suggest pancreatic necrosis and may be alarming. The resulting lack of lipase and insulin are often overlooked. Thus the celiac symptom may have its beginning. Greater care is needed in diagnosis. The "pancreatic mumps" may precede the parotid mumps. In the acute stage probably sulfonamide, penicillin, blood transfusions, reconvalescent serum and arsenic would be of help.

SWEIGERT, C. F., McLAUGHLIN, E. F., AND HEATH, E. M.: *Carcinoma of the pancreas with pulmonary lymphatic carcinomatosis simulating bronchial asthma: case report.* (Ann. Int. Med., Aug. 1947, Vol. 27, 2, 301-307).

A case of a man of 22 is presented in whom the symptoms of bronchial asthma were due to metastatic cancer arising from the pancreas. At first his abdominal symptoms were vague and consisted of a pain in the right upper quadrant relieved by assuming the jack-knife position. X-rays showed a widened duodenal arch and a suggestion of a filling defect on the lesser curvature of the stomach. The chest film showed a disseminated, infiltrating type of density in the lungs. His downward course was rapid. Laparotomy confirmed the pre-operative diagnosis and allowed the insertion of a T-tube in the common duct for drainage.

VEGHELYI, P. V.: *Secondary pancreatitis* (Am. J. Dis. Child., Vol. 74, p. 45, July, 1947).

In a 4 year old child parotitis was followed by a mild pancreatitis and in another child 4 1/2 years old, parotitis was followed by severe pancreatitis. In one case severe pancreatitis followed scarlet fever. These cases show that pancreatitis in children frequently are

complications of certain diseases. The pancreatitis may not be severe enough to be detected. Celiac disease may follow as the result of pancreatic insufficiency. Diagnosis should be made as soon as possible and treatment instituted. Pancreatic extracts must be given to replace the deficiency of pancreatic enzymes. The diet should be low in fat. Vitamins A, D, and K, the fat-soluble vitamins which cannot be absorbed in the absence of lipase, must be administered parenterally.

Liver and Gallbladder

RAWLS, W.B. and ANCONA, V. C.: *The treatment of cirrhosis of the liver with crude liver extract by the intravenous route.* (Rev. Gastroenterology October 1947, Vol. 14, No. 10, 685-692).

The crude liver extract used was Cohn's fraction G², rendered free of pyrogens and toxic amines (Hoagland formula) and was given intravenously properly diluted, at first and for some time, daily, with strict observance of dilutions and speed of administration. The patients also received a diet low in fat, high in carbohydrate and protein. Alcohol was forbidden. Vitamin therapy was instituted when there was clinical evidence of avitaminosis. Surprisingly good results were obtained in early cases and encouraging results even in many rather severe cases. Return of appetite is an indication of improvement. 82 per cent of cases have survived 15 months or longer. Out of a total of 22 cases, 4 have continued treatment-free for periods of 4 to 12 months. It is uncertain why crude liver extract improves these patients.

MORRISON, LESTER M.: *The therapeutic response in chronic nephrosis to treatment for cirrhosis of the liver.* (Rev. Gastroenterology, Sept. 1947, Vol. 14, No. 9, 603-609).

An interesting case of lipid nephrosis associated with multiple myelomata is described in which clinical, hematological and renal improvement followed a regimen similar to that used in cirrhosis of the liver, a diet high in protein and carbohydrate and low in fat, supplemented by injections of crude liver extract, as well as by vitamins of the B-complex group. The author draws some analogies between nephrosis and cirrhosis and believes that this type of treatment ought to be tried on more cases of nephrosis.

Gall Bladder

KUNKEL, H. G., LABRY, D. H., and HOAGLAND, C. L.: *Chronic liver disease following infectious hepatitis 1. Abnormal convalescence from initial attack.* (Annals Int. Med., August 1947, Vol. 27, No. 2, 202-219).

Some cases of infectious hepatitis depart from the usual benign course and persist in showing signs of

liver insufficiency for months or even years following the initial attack. Out of 350 cases, 83 percent recovered from the acute attack in less than 3 months. In the other 17 percent, recovery did not proceed in such a manner and more than 3 months hospitalization was required. These latter cases could be classified into 4 groups — (1) simple relapse with recovery, (2) relapse with transition to chronic hepatitis, (3) chronic hepatitis with persistent bromsulfalein retention and (4) persistent hyperbilirubinemia, symptomatic and asymptomatic. The final outcome of cases with lingering hepatitis is not clear and further follow-up studies are needed to determine whether or not cirrhosis may sometimes be a late result.

Ulcer

KAHRS, T. AND SCHRUMPF, A.: *The results of the medical treatment of peptic ulcer.* (Rev. Gastroenterology, Oct. 1947, Vol. 14, No. 10).

In this paper, which comes from Porsgrunn, Norway, although there is some confusion between X-ray-proved ulcer and "manifest bleeding," nevertheless the statistics from a follow-up study of 220 cases of ulcer cause the authors to believe that the medical treatment of ulcer results in only 21 percent of cures. They advise operation in chronic peptic ulcer when two attempts by medical treatment in hospital have failed to cure. "Cases, however, of bleeding without roentgen symptoms have a marked tendency to heal after medical treatment".

JAMIESON, R. A.: *Perforated peptic ulcer: short term variations in frequency.* (Brit. Med Jour., August 23, 1947, 289-291).

In a very interesting and unusual paper the author studies a large series of cases of perforated peptic ulcer and makes some valuable deductions. Perforations are relatively uncommon in August, September and October and unduly common in December. The comparative reduction of perforations in the autumn may be due to the rest periods of the July vacations. The December peak was not due to over-indulgence at the Christmas period. Perforations are relatively uncommon on Sundays and Mondays and become more common toward the end of the week. This may be related to rest at the weekend. Perforations are uncommon during the night. No evidence was found that perforation was related to the phase of digestion or occurred during strenuous bodily exertion.

ROSSIEN, A. X.: *Protein hydrolysate: a study of effect on peptic ulcer patients during one year.* (Rev. Gastroenterology, Sept. 1947, Vol. 14, No. 9, 623-638).

The author found that the proper administration

of protein hydrolysate to ambulant peptic ulcer patients was useful in correcting constipation, improving the general health, controlling nausea, vomiting, belching, heart-burn, hunger pain, in about 80 per cent of the cases, as well as diarrhea, but that X-ray evidence did not reveal that this method of treatment gave better results than methods previously employed and could not be considered a cure for ulcer. Owing to the fact that the administration of hydrolysate produces a secretagogue effect at the end of an hour, it was found wise to administer an antacid at this time, the author preferring non-reactive aluminum hydroxide gel.

KNIGHT, R. V.: *Bilateral vagotomy: a preliminary report in a case of duodenal ulcer.* (Med. Jour. Australia. Aug. 2, 1947, II, 5, 141-143).

In the case reported, marked reduction of gastric secretion was demonstrated 10 days following the operation; X-ray showed beginning healing of the ulcer and also some delay in gastric emptying time. The author discusses the rationale of the operation, and believes it to be contra-indicated in the presence of acute perforation, acute severe hemorrhage and in cicatricial obstruction.

EXPERIMENTAL MEDICINE

THERAPEUTICS

WELLS, J. J. AND POPP, W. C.: *The use of pyridoxine hydrochloride in the treatment of radiation sickness: preliminary report.* (Proc. Staff Meet. Mayo Clinic, Vol. 22, p. 482, Oct. 14, 1947).

Patients react differently to radiations. Body area treated and dose per field are important. Treatment of extremities has little effect but radiation of trunk may cause considerable reactions. Symptoms of radiation sickness may come on in one-half to three hours after exposure. Malaise, nausea, vomiting and prostration are the chief symptoms.

At least three hypotheses have been advanced in recent years to explain radiation sickness: disturbance of respiratory enzyme systems, capillary dilatation and plasma loss into tissues due to damage by radiation, and hepatic damage and capillary damage by histamine liberated by tissue treated with roentgen rays.

In the present series 200 patients with radiation sickness were treated by intravenous use of pyridoxine hydrochloride (vitamin B₆). Nine per cent of the cases showed excellent results, 55.5 per cent showed good results, 26.0 per cent showed fair results and only 9.5 per cent were not improved. The method was safe and inexpensive and the authors believe that at present this is the best method of treatment.

PATHOLOGY

HALPERN, B. N. AND MARTIN, J.: *Experimental gastric ulcer in guinea pigs: perforation with large doses of histamine when protected by anti-histamine compounds.* (Compt. rend. soc. biol. Paris., V. 140, p. 830, 1946).

Antihistamine compounds which were found effective in guinea pigs in antagonising the bronchial and other effects of histamine were used. Apparently adequately treated guinea pigs were not protected against the ulcerating effects of histamine: single large doses proved fatal in 24 hours.

COLE, F., BARONOFSKY, I. D., AND WANGERSTEEN, O. H.: *Curare and shock: the production of hemorrhage into the upper intestine of the dog with large doses of curare.* (Surgery, V. 21, p. 881, 1947).

Curare in large doses (Intoeostrin, 0.71 to 1.24 cc. per pound body weight) when given intravenously to dogs under pulmonary ventilation resulted in the production in 2 to 5 hours of hemorrhage into the intestine. Gastric secretion was not stimulated and exclusion of gastric juice did not prevent the intestinal mucosa hemorrhages. Gross congestion was not produced in the intestinal mucosa by topical application of curare. Shock was present in the curare injected animals. When shock was averted by vasoconstrictor drugs and blood transfusions, the intestinal hemorrhages were not seen. It, therefore, appears that the hemorrhages were the result of shock rather than a specific reaction to curare.

MORRIONE, T. G.: *Quantitative study of collagen content in experimental cirrhosis.* (J. Exper. Med., V. 85, p. 217, March 1947).

Hepatic cirrhosis was produced in rats with carbon tetrachloride and p-dimethylaminoazobenzene. The hepatic collagen content in 15 normal rats was 0.23 per cent wet weight. Rats on the "butter yellow" diet for five months showed a well developed cirrhosis and the collagen rose to twice its normal value of 47.5 mg. per liver. Histologically the collagen was mostly in the periportal regions. When the rats were not sacrificed but put on a normal diet, there was a fall in the collagen content to 28.3 mg. per liver in six weeks. When carbon tetrachloride was used the average collagen content rose to 1.01 per cent or 86.4 mg. per liver due to advanced cirrhosis, as seen microscopically. Decrease in collagen content after discontinuing the inhalations of carbon tetrachloride was slow and incomplete, but was greatest in the first month during which it fell from 10.01 per cent to 0.69 per cent (73.7 mg.). The decrease was commensurate with that seen microscopically with a reticulum stain.

SHAIRER, E.: *Spectrographic analyses of the elementary composition of human concretions, particularly the gall stones.* (Virchow's Arch. path. Anat. Physiol. V. 312, p. 534, 1944).

Various concretions of the human body, including 271 gall stones and 30 renal stones, were subjected to spectrographic analysis. The elementary composition of stones from different regions and different periods were similar though in general elements were highest in stones showing greatest pigmentation. The commonest trace elements found were lead, silver, aluminum, boron, cadmium, iron, manganese, copper, and zinc. These occurred in addition to the usual elements found composing concretions (calcium, phosphorus, etc.).

MORRIS, C. R., GROSSMAN, M. I. AND IVY, A. C.: *Failure of "enterogastrone" to prevent rumenal ulcers in the Shay rat.* (Am. J. Physiol., V. 148, p. 382, Feb. 1947).

Pyloric ligation results in formation of ulcers of the rat's gastric rumen. Enterogastrone was administered parenterally in relatively large doses for as long as 30 days to such rats. The enterogastrone did not prevent the formation of the rumenal ulcers. The ulcers are multiple: the dose and length of treatment could not be correlated with the number of ulcers.

BERG, B. N.: *Gastric ulcers produced experimentally by vascular ligation.* (Arch. Surg., V. 54, p. 58, Jan. 1947).

The fundus and the antrum of the rat's stomach are supplied by separate arteries so that the blood supply to each of these segments of the stomach may be interrupted by ligation of the corresponding arteries. Ligation of the blood vessels results in ulcerations of the stomach region affected. The lesions appear to be infarcts. The ulcerated area is determined as to size and depth by the extent to which collateral circulation is established. Even when the ulcerations are extensive the rats may survive. It was concluded that enzyme action is not involved in the formation of the ulcers.

SINAIKO, E. S. AND NECHELES, H.: *Experiments in ulcerative enteritis.* (Surgery, V. 20, p. 395, 1946).

Poppe reported the production of ulcerative colitis by obliteration of the mesenteric lymphatics in the dog. The experiments of Poppe were repeated but the results could not be confirmed. On the injection of obstructing agents such as bismuth oxychloride or

sorcin into the lymphatics there resulted acute inflammatory changes in the whole bowel. After the acute phases subsided only a thickened bowel wall was seen. The authors think that Poppe's results could be attributed to a vascular thrombosis rather than lymphatic obstruction.

PHYSIOLOGY

PHILLIPSON, A. T.: *The production of fatty acids in the alimentary tract of the dog.* (J. Exp. Biol., Vol. 23, p. 346, 1947).

Volatile fatty acids are present in greatest concentration in the venous blood from the large intestine. Blood samples taken from other regions were exceeded in concentration of volatile fatty acids by the large bowel venous blood, consequently this is evidence that volatile fatty acids are absorbed. Determinations made on the gastrointestinal contents showed volatile acids only in the ingesta of the large bowel. Propionic, acetic, and butyric acids were identified. Propionic acid producing bacteria are probably normal inhabitants of the large intestine of the dog.

HWANG, K., ESSEX, H. E. AND MANN, F. C.: *A study of certain problems resulting from vagotomy in dogs with special reference to emesis.* (Am. J. Physiol., 149: 429, May, 1947).

Trained adult dogs were used to study the effects of vagotomy at different levels from the diaphragm to the larynx. Both vagi were cut. Balloons inflated within the esophagus or barium meals were used as agents for studying the functional results. When vagotomy was performed at or above the level of the lung hilus, regurgitation and emesis was a frequent result, and it was found that there was a complete loss of peristaltic activity of the lower two-thirds of the esophagus when vagotomy was done at any level above the aortic arch. The mere retention of food in the paralyzed esophagus, or distention, was not shown to be the cause of the vomiting, but apparently was induced by a more excitable status of the vomiting center as judged by the response to apomorphine. Proaine blocking of vagus nerve stumps did not alter this increased sensitivity. Complete sympathectomy in two dogs did not show any significant change of function of the esophagus and cardia and only slight reduction of tone of the cardia in a third dog. These three dogs died on the second or third day. The tone of the cardia was never increased after vagotomy, but was reduced to different degrees in the majority of cases. It is likely that the vagus contains both motor and inhibitory fibers to the cardia, and that the inhibitory fibers branch off above the level of the arch of the aorta to take an intrinsic course in the wall.

OLSEN, N. S. AND KLEIN, J. R.: *Hyperglycemia induced by certain insulin preparations.* (Proc. Soc. Exp. Biol. Med., V. 66, p. 86, Oct. 1947).

All commercial preparations of insulin, except the Danish NOVO brand, on intravenous administration first increased blood glucose concentration. The maximum increase occurred in 5 to 10 minutes. After 20 to 30 minutes the glucose concentration returned to pre-injection levels, and then continued to fall, leading soon to hypoglycemia. As little as 0.1 unit insulin per kilogram body weight had a definite hyperglycemic effect though it was more pronounced with 1 unit per kilogram. The effect was independent of blood glucose levels and could be produced when blood sugar was high as well as when low. The hyperglycemic effect of insulin could be observed only after intravenous administration. The transitory hyperglycemia could be obtained with both crystalline and amorphous preparations.

DARBY, W. J., KASER, M. M. AND JONES, E.: *Influence of pteroylglutamic acid on absorption of vitamin A and carotene in patients with sprue.* (J. Nutrit., V. 33, p. 243, Feb. 1947).

Four patients with sprue, kept on their usual diets without additional carotene or vitamin A, were given pteroylglutamic acid, 5 to 15 mg. per day, by mouth or intramuscular route. With administration of pteroylglutamic acid the low serum carotene levels rose, while withholding resulted in a relapse. The evidence would favor the conclusion that pteroylglutamic acid plays an important role in the physiology of the digestive tract and is concerned in the absorption of fat soluble substances from the intestine.

PHARMACOLOGY

LEATHEM, J. H. AND SEELY, R. D.: *Plasma and liver protein concentrations of rats fed thiouracil.* (Am. J. Physiol., V. 149, p. 561, 1947).

Male rats were fed 0.5 per cent thiouracil for a period of 20 to 25 days. Total plasma protein nitrogen, plasma non-protein nitrogen and plasma globulin concentrations were increased but plasma albumin concentrations were the same as the controls. The thiouracil fed rats reduced their food intake and lost body weight but nevertheless their livers were heavier than those of the controls. The weights of the pituitary and adrenals and of the kidneys were not affected. The hematocrit values were lower.

SCHEIFLY, C. H.: *Pentothal sodium; its use in the presence of hepatic disease.* (Anesthesiol., V. 7, p. 263, 1947).

Various anesthetics have been known to have a di-

rect hepatotoxic effect. The liver participates in the detoxification of certain anesthetics. In rats the removal of large portions of the liver results in prolongation of the anesthetic action of sodium pentobarbital but not sodium pentothal. These results suggest that the liver protects against sodium pentobarbital by detoxifying it but has no effect on sodium pentothal. Apparently detoxification of the latter is non-hepatic. It is therefore concluded that sodium pentothal would be a safe anesthetic to employ in patients with liver damage.

SURGERY

GILBERT, J. A. L. AND DUNLOP, D. N.: *Hypoglycemia following partial gastrectomy.* (Brit. Med. Journ., Aug. 30, 1947, 330-332).

In a follow-up of 45 consecutive patients on whom a partial gastrectomy had been done for peptic ulcer, it was found that in 17 cases there occurred post-operatively and for months, symptoms of dizziness, palpitation, sweating, epigastric discomfort and a feeling of weakness which, in several instances, progressed to complete loss of consciousness. These symptoms coming on from one-half to one and a half hours after eating were rapidly relieved by taking sugar or other easily assimilable carbohydrate. Blood sugar tolerance tests showed an initial high rise of sugar followed soon by a rapid and precipitous drop, frequently to as low as 60 mgm. percent. The explanation apparently is to be found in the fact that the reduced stomach "dumps" its food too quickly into the bowel, producing a sudden rise in blood sugar which in turn conditions the pancreas to secrete large amounts of insulin. The syndrome has been produced by introducing glucose into the duodenum by an indwelling tube. Relief may be obtained by slowing the emptying time of the stomach remnant by giving one ounce of olive oil before meals. Ephedrine in 1/2 grain doses half an hour before meals also flattens the post-prandial blood sugar curve. For some reason, as the authors state, there has been a strange and unprofitable silence in British medical literature to the subject of post-gastrectomy hypoglycemia, while anemia and other features have received appropriate consideration.

BAUMEL, J. AND HERMANN, G.: *Les tumeurs vilieuses du rectum generatrices de cancers rectaux.* (Acta G. E. Belgica, Mar. 1947, X, 3, 89-103).

This is a plea, well documented by case reports, for the surgical removal of rectal papillomatous tumors before they have undergone cancerous degeneration. The tumors, prior to malignant transformation, are

essentially benign, and can be followed by rectoscopic examination and removed by an ambulatory operation which is not mutilating or dangerous.

KINSELLA, V. T.: *Post-operative flatulence or "gas" pains.* (Med. J. Australia, April 26, 1947, I, 17, 528-529).

A strong plea, written with intense feeling, against the use of laxatives before and after abdominal operations. To avoid "gas" pains the author regards the use of non-residue feeding before and after operation as of highest value as a preventative.

RAVEN, R. W.: *Partial hepatectomy and right hemicolectomy for carcinoma of the hepatic flexure.* (Brit. Med. Journ., August 16, 1947, 249-250).

The author directs attention to the operation of partial hepatectomy combined with right hemicolectomy for carcinoma of the hepatic flexure of the colon infiltrating the right lobe of the liver. A case is reported in whom this operation was successfully performed and another who is alive six years after resection of the anterior aspect of the right hepatic lobe combined with right hemicolectomy for cancer of the hepatic flexure of the colon.

BLAIN, ALEXANDER, III.: *Penicillin in experimental intestinal obstruction.* (Alexander Blain Hosp. Bull., August 1947, Vol. 6, No. 3, 107-114).

Completely obstructed and strangulated gut produced experimentally in dogs, caused early death from peritonitis when untreated. By using penicillin in massive doses, death was delayed. By using also curative surgery and blood transfusions in addition to the penicillin, recovery was obtained usually even 72 hours after obstruction. A plea is made to use penicillin in human intestinal obstruction.

BLAIN, A. AND HARKINS, H. N.: *Intestinal obstruction due to perforations of the gall bladder.* (Alexander Blain Hosp. Bull., August, 1947, Vol. 6, No. 3, 79-106).

Intestinal obstructions of obscure origin may sometimes be due to perforations of the gall bladder. In this series, one-fourth of such perforations resulted in intestinal obstruction. In puzzling cases, gall bladder disease should be considered in order that intestinal obstruction produced by gall bladder perforation may not be overlooked. In this series, intestinal obstruction due to gall bladder perforations was more often due to acute or subacute perforations with resultant inflammatory paralytic or mechanical obstruction than to

chronic perforations with resultant classical gall stone ileus.

BRUNSCHWIG, A.: *Cancer of the pancreas.* (Illinois Med. Jour., August 1947, Vol. 92, No. 2, 82-85).

Although, as Moynihan stated, surgery of the pancreas did not exist in 1926, today the pancreas has been brought within surgical reach. Even total pancreatectomy can be done and renders the patient only slightly diabetic, so that he requires merely 20 to 40 units of insulin daily. In cancer of the head of the pancreas, a pancreateo-duodenectomy is performed in one stage and the lower fourth of the stomach removed. Continuity is re-established by gastrojejunostomy, choledcho-cholecysto-jejunostomy and enteroenterostomy. Pancreatin is used where fat in digestion results. Mortality figures are not given.

WALTERS, W., COUNSELLER, V. S., WAUGH, J. M. AND CLAGETT, O. T.: *Report of surgery of the stomach and duodenum for 1945* (Proc. Staff Meet. Mayo Clinic, August 20, 1947, Vol. 22, No. 17, 345-349).

Since 1931 the number of cases with duodenal ulcer treated surgically has decreased from 26 percent to 13 percent. The authors' figures are from the Mayo Clinic. They believe this decline indicates that surgery is not employed frequently enough. In the performance of partial gastrectomy 241 times for chronic duodenal ulcer, the hospital mortality rate was only 1.7 percent and among 80 patients who underwent posterior gastro-enterostomy for chronic duodenal ulcer, the mortality rate was only 1.2 percent. Partial gastrectomy for gastric ulcer is apparently curative, without recurrences and carried a mortality of only 2.1 percent. Resection for gastro-jejunal ulcer showed a mortality of 3 percent. Partial gastrectomy for malignant lesions of the stomach showed only 3.2 percent hospital mortality. Total gastrectomy was done 24 times with four deaths.

DUCKETT, J. W.: *Surgical management of congenital hypertrophic pyloric stenosis.* (Texas State J. M., September, 1947, XLIII, 5, 320-324).

The operation of Fredet-Ramstedt still remains as the accepted and standard operation and results are excellent. The article is a plea for operation as soon as the diagnosis can be safely made on the symptoms — projectile vomiting, visible peristaltic waves and the presence of a pyloric tumor. The most important X-ray sign is a narrowed prepyloric canal, while the emptying time of the stomach is of no practical assistance. Pre-operative and post-operative care is detailed and the operation described.

METABOLISM AND NUTRITION

SCHERWIN, J.: *Idiopathic hypoprothrombinemia refractory to vitamin K.* (Nordisk Med., May 16, 1947. 20, 34, 1157-1158).

This is a report of a case of idiopathic hypoprothrombinemia in a woman aged 34. In 1944 she responded well to vitamin K, but in 1946 the reaction was absent even in case of very large doses. The absence of prothrombin-supporting factors could not be demonstrated, nor the presence of abnormal quantities of coagulation-inhibiting substances. The remaining coagulation examinations were normal, and there were no signs of disorders of the liver or alimentary tract, apart from achylia which has not been diagnosed with certainty.

NISSEN, H. A.: *Gout.* (Journal-Lancet, LXVII, 7, July 1947, 269-270).

By analyzing 1500 patients diagnosed as arthritis, the author found 251 whom he diagnosed as gout, in all of whom the blood uric acid exceeded 4.0 mgm. percent. They were characterized by exacerbations as a rule, though in some cases pain was continuous. They responded to intravenous injections of sodium salicylate, sodium iodide and colchicine. It is not necessary to have the classical symptoms such as tophi, passage of urate stone or family history of gout to make the diagnosis.

DEVINE, J.: *An unusual first symptom of goiter.* (Med. J. Australia, I, 20, May 17, 1947, 618-619).

The patient complained only of the fact that her glass eye was falling out. A toxic goiter was found and resected. Within a week following operation, the glass eye could be seen settling farther back in the orbit, due to a reduction in the size of the orbital fat pad. A new glass eye had to be obtained. This case suggests the primary importance which must be attached to the role of retro-orbital fat in the production of exophthalmos in goiter.

R. L. HERNANDEZ BEGUERIE, AND TOM D. SPIES.: *Roentgenological studies on the effect of synthetic folic acid on the gastro-intestinal tract of patients with tropical sprue.* (Am. J. Roentgen. & Radium Therapy, 56, 3, 337. September 1946).

To make the diagnosis of tropical sprue, the following symptoms should be present: Glossitis. Diarr-

hea, characterized by voluminous, foul smelling, frothy, liquid, yellow stools. The fat content of the stools must be increased. A body weight loss of at least 20 lbs. must have occurred during the six months preceding the initiation of this study. There must be a macrocytic anemia with a red blood count of less than 2.5 millions and a color index of 1.0 or more. The bone marrow must show a megaloblastic arrest. The gastric juice must contain free HCl on fractional analysis after histamine stimulation. The oral glucose tolerance curve must be flat. The blood calcium level must not be below 8.5 mg per cent. The serum amylase and lipase activity must be normal. All four reported patients had no specific therapy within the five weeks preceding this study.

The authors report four patients selected according to these criteria. Their conclusions are that synthetic folic acid in daily doses of 10 mg. has a profound effect on the alimentary tract function of patients with tropical sprue in relapse. Repeated roentgen studies on one case, who did not receive folic acid, showed no improvement within a similar period of time. In contrast to this positive control, two other cases showed striking improvement which was evidenced by return of intestinal motility toward normal and the establishment of a continuous column of barium which was not interrupted by segmentation or fragmentation. The roentgenographic findings most often observed in this series of patients with tropical sprue are mucosal edema, intestinal segmentation with alternation of intestinal spasm and dilatation and intestinal hypomotility. These abnormal roentgenological patterns could very well be the result of nutritional disorder, hypoproteinemia, disease of the liver, disease of the mesentery, or any disease condition which may produce submucosal edema, but in these cases the response to synthetic folic acid was dramatic.

FRANZ J. LUST

BENJAMIN, S.: *The psychosomatic phase in the management of diabetes mellitus in adolescents and young adults.* (Med. Ann. Dist. Columbia, July 1947, Vol. 16, No. 7, 361-365).

The prolonged life expectancy of diabetics due to the advent of insulin has given rise to many psychosomatic problems which were not apparent before. Now that diabetics have an increased life expectancy it is of great importance that they be properly educated in their mental approach. A fatalistic attitude that they cannot enjoy normal activities and a normal married life may lead them to non-coöperation, revolt and possibly psychic disturbances. Ideally, this educative process should start as soon as the diabetes is diagnosed. It is the physician's responsibility to encourage the development of a healthful mental attitude by informing the patient that practically the only restriction is dietary, and in cases in which it is necessary dietary

supplemented by a regulated insulin régime. While diabetics who plan to have children should not marry other diabetics or mates with diabetic backgrounds, marriage to non-diabetics will lead to normal married lives and children.

It is important, where patients have been previously misinformed concerning their future outlook, that they be appraised of this misinformation for earliest correction. A diabetic who has been properly instructed and in whom a good psychologic balance has been established is more likely to be coöperative and amenable to control.

TROWELL, H. C.: *Tropical macrocytic anemia and nutritional macrocytic anemia*. (S. African J. Med. Sci., Jan. 1947, Vol. 12 No. 1, 21-32).

A review is offered of the macrocytic anemias, of obscure origin, encountered in the tropics. There is thus tropical macrocytic anemia encountered in pregnant women and nutritional macrocytic anemia encountered in both sexes, and at all ages, but not in connection with pregnancy. It is by no means certain whether any point, apart from pregnancy, constitutes a valid point of distinction between these two anemias. It is not certain that there is any valid point of distinction between the tropical macrocytic anemia of pregnant women in warm climates and the macrocytic anemia of pregnancy seen in temperate regions. Two points are, at present, largely the cause of the uncertainty; firstly the blood picture, especially the bone marrow picture, is not clearly described in the tropical anemia; and secondly, if critically examined, the majority of the tropical cases have a light helminthic infection or mild relapsing malaria, which many contribute to the anemia, and confuse its picture.

Personal observations are offered on 63 cases of anemia, 6 of whom were pregnant, investigated in Uganda, and treated by iron, and by various liver solutions of American origin. The etiology of anemia in any single case is almost always multiple, hookworms can usually be detected if stool examinations are repeated and employ a concentration technique (thus 80% were infected) similarly if repeated blood slides are examined relapsing attacks of malaria can often be detected where there is no evidence for this on admission (thus 31% were infected). With regard to the deficiencies present most cases show a dual deficiency not clear cut and cannot always be predicted from the hematological data: thus macrocytic orthochromic anemia may be refractory to liver, but react to iron, although usually the response is otherwise.

Unit for unit the crudely concentrated liver solutions are always more effective than the more refined and concentrated solutions, neither are as effective as would be expected in pernicious anemia.

Those who cannot employ full hematological investigation should consider carefully the appearance

of a carefully spread thin blood film. Where this dual deficiency is present the picture is neither that of hypochromic cells displaying little anisocytosis (pure iron deficiency) nor evenly stained, flattened cells, showing much anisocytosis (pure P.A. deficiency). In "dimorphic anemia" the central fields display solid looking cells, perforated with one or more vacuoles, interspersed with a few densely stained, thickened cells, and moderate increase of anisocytosis; peripheral fields show a few thickened cells and many flat cells which are evenly stained and there is increased anisocytosis. This is the hall-mark of the dual deficiency that has been called "dimorphic anemia."

ZIMMERMAN, F. T., BURGEMEISTER, B. B. AND PUTNAM, T. J.: *A group study of the effect of glutamic acid upon mental functioning in children and adolescents*. (Psychosomatic Med., May-June 1947, IX, 3, 175-183).

The rationale for the oral administration of 1 (+) - glutamic acid in the treatment of defective mental functioning is based upon a number of experiments which indicate a particular relationship to cerebral metabolism. Glutamic acid is the only amino acid capable of maintaining the oxygen uptake of sliced brain tissue. Electrical charges during nerve activity have been shown to be intrinsically connected with the release of acetylcholine. The enzyme, choline acetylase, when inactivated by dialysis, is reactivated by the addition of 1 (+) - glutamic acid.

The experiments showed that the administration of glutamic acid accelerated mental functioning in human subjects, most strikingly in the seriously retarded group.

It is possible that these observed effects of glutamic acid are somehow related to the formation of acetylcholine. The experiments are being continued to determine the ceiling effect of glutamic acid upon intelligence.

SELIGER, R. V.: *Religious and similar experiences and revelations in patients with alcoholic problems*. (Southern Med. and Surgery, August 1947, Vol. 109, No. 8, 265-266).

A Fellow of the American Psychiatric Association and Medical Director of the Neuro-psychiatric Institute of Baltimore, recites 3 cases of alcoholics who were apparently cured of their habit as the result of "religious" experiences. In all three cases, "the impulse of the new idea" is obvious. The author regards true religious conversion as resulting in altruism of an active type. In two of the cases although apparent cure resulted, there was considerable dissociation of the personality at the moment of decision.

YOUNG, R. C.: *The role of the private psychiatric hospital in the treatment of alcoholic addicts.* (Jour. Arkansas Med. Soc., Sept. 1947, XLIV, 4, 91-93).

The author finds that regulated amounts of whisky, given initially over a period of four or five days, along with mild sedatives and proper elimination, show better results than abrupt withdrawal. He regrets that physicians are turning over so many of their cases to lay organizations. Among the other interesting observations are the following — although it is the most important meal, 85 per cent of alcoholics eat no breakfast; barbiturates must be used with great caution; benzedrine sulfate has no place in the treatment of alcoholics; amino-acids by parenteral injection give promise of great aid to the markedly under-nourished alcoholic; all alcoholics (except those cases caused by mental disease) can get well and stay well once they accept the fact that under all circumstances they cannot take a drink the rest of their lives.

BENSON, R. A. AND KIMBALL, F. T.: *A comparison of cereals and their value in the feeding of infants and children.* (Arch. Pediatrics, Vol. 64, No. 9, 476-479).

A comparison of the nutritive value and digestibility of the various cereals used for children is timely, inasmuch as pediatricists begin cereal feedings at least six months earlier in life than was formerly the custom. Cream of rice, a highly-milled product, was found to exceed all other market products in available total carbohydrates and to contain less roughage than any. Although it is low in protein and fat, its advantages as an energy food become obvious.

WOOD, G. T.: *Hyperthyroidism and diabetes.* (Southern Med. & Surg., August 1947, Vol. 109, No. 8, p. 261-263).

The author shows that hyperthyroidism and diabetes are antagonistic, and that insulin and thyroxin also exert antagonistic effects. Some cases of hyperthyroidism show glycosuria which is not true diabetes. The two diseases are occasionally associated: There is an incidence of 1.52 per cent of hyperthyroidism in diabetes, while 3.15 per cent of patients operated on for thyroid disease show diabetes. In other words, diabetes seldom precedes hyperthyroidism, whereas hyperthyroidism preceding diabetes is more than twice as common. The details of a case are given in which thyroid resection cured hyperthyroidism without much effect on the diabetes. The discussion deals chiefly with surgical details.

BRUNSTING, L. A. AND MASON, H. L.: *Porphyria with cutaneous manifestations.* (Proc. Staff Meet. Mayo Clinic, Oct. 29, 1947, Vol. 22, 502-504).

Porphyria may become manifest for the first time in adult life in the form of a bullous eruption of the light-exposed surfaces of the skin. Four illustrative cases are presented in which chronic alcoholism as well as hepatic dysfunction seemed to have been precipitating factors. The general health of the patients improved under an anticirrhotic regimen. The syndrome under consideration represents the tardive phase of congenital porphyria with essentially benign and chronic symptoms, although in one case the characteristic clinical and laboratory features of so-called acute porphyria occurred. Microscopically, the affected skin showed, in the connective tissue, changes resembling those of senile elastosis. Reactions of photosensitivity could not be artificially reproduced. The results of quantitative analysis of the urinary porphyrins are presented. Surveys of the family in two cases brought to light two instances of a condition of latent porphyria in apparently normal individuals.

WHITFIELD, R. G. S.: *Anomalous manifestations of malnutrition in Japanese Prison Camp.* (Brit. Med. Journ., Aug. 2, 1947, 164-168).

Three conditions arising from malnutrition are described which did not behave in the manner laid down in textbooks.

On a diet of polished white rice, pantothenic acid deficiency with an accompanying peripheral neuritis was the chief trouble.

On a barley and bean diet, cardiac beriberi occurred with some pantothenic acid deficiency and a slightly different neuritis.

At no time was a typical case of dry beriberi seen. A series of four cases of epileptiform seizures of unknown causation is described. The wise humility of such authorities on deficiency diseases as Stannus is supported by clinical observations. Unknown or ill-defined deficiency diseases probably far outnumber those whose characteristics are already plainly established.

MELLANBY, SIR EDWARD: *Further observations on the production of canine hysteria by flour treated with nitrogen trichloride ("Agene" process).* (Brit. Med. Journ., Saturday, August 23, 1947, 288-289).

It was shown that wheat flour "improved" by the so-called "agene" process produced, when eaten by dogs, the condition known as canine hysteria, or, in the U. S. A., as running fits. Untreated flour from the same grist produced no such fits and when it replaced the treated flour in the diet, the fits stopped. In the experiments carried out, the flour was agenized

to the extent of 8 grams of nitrogen trichloride to 280 lbs. of flour. This is an ordinary degree of treatment of flour used for human consumption. Rats and mice fed on agenized flour did not show the nervous symptoms that dogs showed, but it was found that ferrets were susceptible and, when severely affected, developed true epileptiform fits.

BARSI, I.: *A new treatment of rheumatoid arthritis.* (Brit. Med. Jour., Aug. 16, 1947, 252-253).

Selecting chronic cases of rheumatoid arthritis, this Budapest physician gave 300 cc. blood transfusions using pregnant women as donors. Improvement took place rapidly in some of the cases, and seemed to be lasting. This work is suggestive from a research standpoint. It has been observed for some time that dramatic improvement occurs at times in patients with rheumatoid arthritis who become pregnant.

WOLPE, L. Z.: *A three year review of statistics for milk substitutes in the treatment of infantile eczema.* (Arch. Pediat., August 1947, Vol. 64, No. 8, 399-402).

Of an original list of over 100 milk substitutes, nine were selected for use in the eczema ward at the Los Angeles County Hospital since 1941, under the direction of the author. The present study evaluates the progress made with a group of babies fed milk and given routine eczema therapy, as well as a group of babies fed milk substitutes given the same therapy. Patients fed milk substitutes reached clinical relief faster than those fed on a milk dietary. While both milk and milk substitute groups showed a substantial increase in weight, the experience for the milk fed group was slightly better, the difference is not significant.

WILSON, D.: *Poisoning by Inocybe Fastigiata.* (Brit. Med. Journ., August 23, 1947, page 297).

Three patients after eating the fungus (gathered by mistake for mushrooms) immediately developed toxic symptoms as follows — blurred vision, salivation, sweating, dizziness, sluggish pupils, abdominal soreness, sometimes abdominal rigidity, diarrhea, nausea, vomiting. Treatment consisted of the immediate administration of 1/50 gr. of atropine sulfate, thorough gastric lavage and 2 ounces of magnesium sulfate.

Within two hours all symptoms of poisoning had disappeared and convalescence was uneventful. In cases of fungus poisoning where the symptoms appear within one or two hours, the symptoms are due to *muscarine*, which is contained in *Amanita muscaria*, *Amanita pantherina* and many species of *Inocybe*. Atropine is a specific antidote for muscarine.

MISCELLANEOUS

YOUNGMAN, N. V.: *Psychological aspects of the early diagnosis of cancer.* (Med. J. Australia, I, 19, 581-587).

A psychiatrist studies 50 patients with cancer attending the Radium Institute to discover why the majority come for treatment too late. The reasons are many and relate to family, financial and social life, as well as to lack of intelligence, fear and the scarcity of symptoms so often found in early growths. Medical mismanagement was responsible in a few cases. The aged are tardy in this, as in other matters. The author recommends that his study be extended to larger numbers of cases, since time is of the essence in early treatment, but he seems to be pessimistic about efforts aimed at earlier treatment and points out the obvious lack of logic in campaigns to heighten cancer consciousness when we have, after all, not too much to offer in the way of cure.

MURLESS, B. C.: *Hernia of the diaphragm as a complication of labor.* (Brit. Med. J., Aug. 16, 1947, 251-252).

Two cases of true diaphragmatic hernia and one of eventration of the diaphragm complicating pregnancy are described for the purpose of showing that labor may be permitted to proceed with safety under such conditions and catastrophic effects do not occur. Symptoms cease after delivery and it seems probable that such herniae are cured by relief of the intra-abdominal pressure.

RUSKIN, A.: *Therapy of essential hypertension.* (Texas State M. J., Sept. 1947, XLIII, 5, 325-327).

The author notes that sudden cold weather elevates blood pressure in patients seen at the Hypertensive Clinic. Important is his observation that many persons presenting wide fluctuations in blood pressure from normal (120/80) to high levels of hypertension (for example, 200/120) may go on for years and even dec-

ades with surprising lack of cardiac, renal or cerebral involvement. Transient hypertension seen in persons wounded in the recent Texas City disaster lasting from several hours to several days, probably was on a nervous basis. In special experiments with various drugs on persons with uncomplicated hypertension, the author (with McKinley) noted symptomatic relief from the use of all drugs tried except potassium thiocyanate, and these included phenobarbital, mannitol hexanitrate, glucophylline, niacin, and such placebos as lactose or sodium bicarbonate. The blood pressure-lowering effects of potassium thiocyanate were greater than those of other drugs, but the thiocyanate was unpleasantly toxic. Drug therapy is justifiable for symptomatic relief. In hypertensive encephalopathy crises, all possible therapeutic methods ought to be considered. We must face the fact, however, that no satisfactory treatment exists for hypertension.

WARTER, P. S., BETTS, R. W., AND HOROSCHAK, S.: *The gastrointestinal tract and nutrition in rheumatoid arthritis*. (Rev. Gastroenterology, Sept. 1947, Vol. 9, 617-623).

This is a report on the effects of giving patients with rheumatoid arthritis supplemental feedings of protein and yeast hydrolysate (Aminovite). There occurred some weight increase and some improvement in the blood counts in the majority of the cases. There was reduction of edema around the joints in some of the patients. The treatment also included either gold therapy or injections of strepto-staphylococcus vaccine toxoid. The treatment was obviously of considerable value and led the authors to speculate upon the etiology of the disease, stressing the possible importance of a poor protein intake in the presence of a chronic focus of infection.

REICH, C.: *The hematological aspects of gastrointestinal disease* (Rev. Gastroenterology, Sept. 1947, Vol. 14, No. 9, 615-617).

In a brief review of the subject, the various causes of anemias, as they arise from digestive diseases, are

mentioned — hemorrhage from various lesions produces an anemia whose features depend on the suddenness or chronicity of the bleeding; faulty absorption of hematopoietic factors may cause either a hypochromic or hyperchromic anemia; in sprue, celiac disease and idiopathic steatorrhea usually are associated with a macrocytic anemia. Carcinoma of the stomach may not produce anemia at all, or it may be associated with a macrocytic, microcytic or normocytic anemia, depending upon whether hemorrhage or failure of absorption dominate the picture.

JONES, G. E., CHALECKE, W. E., DEC, J., SCHILLING, J. A., RAMSEY, G. H., ROBERTSON, H. D., AND STRAIN, W. H.: *Iodinated organic compounds as contrast media for radiological diagnosis. VII: Studies on tetraiodophthalimidoethanol as a medium for gastrointestinal visualization*. (Radiology, August 1947, Vol. 49, No. 2, 143-151).

Comparative studies in dogs of barium sulfate suspensions and of tetraiodophthalimidoethanol suspensions show that the iodinated medium gives more complete and more accurate delineation of experimentally produced stomach lesions. Double contrast enema studies in dogs were similarly much more satisfactory with the iodinated organic medium than with barium sulfate. A limited clinical experience with tetraiodophthalimidoethanol has shown that the new medium is more palatable than barium sulfate, and apparently as safe to use. Further use of the new medium is dependent on the outcome of critical comparisons with barium sulfate in selected clinical cases.

ELLINGER, P. AND HARDWICK, S. W.: *The nicotinamide saturation test*. (Brit. Med. J., May 17, 1947, 672-676).

The authors describe extended nicotinamide feeding experiments on normal persons and pellagrins, which provide evidence that lack of "methyl-donators" may affect the results of a nicotinamide-satura-

tion test. The new test described avoids this error.

GAULD, W. R. AND LYALL, A.: *Tuberculosis as a complication of diabetes mellitus*. (Brit. Med. J., May 17, 1947, 677-679).

17 cases of diabetes mellitus and tuberculosis are described. Poorly controlled diabetes predisposes to tuberculosis and causes a rapid spread of the disease. Routine radiography in diabetics should be undertaken. The incidence of T. B. in diabetes has always been very high.

MURISON, A. R., SUTHERLAND, J. W. AND WILLIAMSON, A. M.: *DeMorgan's Spots*. (Brit. Med. J., May 10, 1947, 634-636).

The minute round ruby-colored macules known as DeMorgan's spots are common in adults, especially in the skin of the abdominal wall, varying in size up to a diameter of 5 mm. and having the microscopic

character of simple hemangiomata. The authors found by observations on 1300 patients that the incidence rises from 5 percent in adolescence to 75 percent at 70 years of age. They were slightly more common in malignant than in non-malignant disease but not sufficiently so to be of diagnostic importance.

PORTEOUS, W. M.: *Visceral zoster. Report of a case*. (New Zealand Med. J., April, 1947, XLVI, 252, 106-108).

Reference is made to an association of herpes zoster in angina pectoris; zoster of the left buttocks duplicating itself on the inner wall of the urinary bladder; of zoster of the chest affecting the subjacent pleura; and of functional changes in the duodenum and stomach associated with primary herpes of the dorsal segments. His own case was one of zoster along the course of the right tenth thoracic nerve associated with some gastric hemorrhage, assumed to be due to an ulcer which perforated and led to a circumscribed peritoneal abscess with eventual recovery.

Degenerative Vascular Lesions and Diabetes Mellitus

By
ERNEST B. MILLARD, M.D.
and
HOWARD F. ROOT, M.D.
BOSTON, MASSACHUSETTS

INTRODUCTION

THE CAUSES of death in diabetic patients have undergone a marked change since Naunyn published his classic description of the disease at the turn of the present century (1). He reported 49 patients with autopsies, of which 13 died in diabetic coma and 19 of tuberculosis. Only four died of arteriosclerotic disease. Moreover, the average duration of the disease, was only 2.6 years. Only two patients lived over 10 years with diabetes.

Of 527 diabetic autopsies performed between 1923 and 1938 reported by Warren in 21 per cent the duration was over ten years. In the present series, the patients lived an average per cent of 9.8 years, with 51 per cent exceeding ten years. This was longer than in previously reported series of diabetic autopsies (Warren), but still considerably below the life expectation of normal persons. Coma and tuberculosis were rare causes of death, but about two-thirds of the series succumbed to arteriosclerotic disease. In the future, new forms of treatment and the recognition of extrapancreatic factors in the disease may again change the predominating pathological findings and the present emphatic role of premature arteriosclerosis may be modified.

A study of diabetic autopsies in hospital patients includes the most gravely complicated cases and, therefore, gives a one-sided view of diabetes. Against this background should be considered the great number of mild, living cases, still outside the hospital. However, it is only by comparison of autopsied cases that the influence of changing types of treatment, duration of the disease and other factors, upon the course of the disease and its complications may be assessed.

This present series includes diabetic patients who came to postmortem examination at the New England Deaconess Hospital in the years 1940 through 1945. The group includes cases of unusual duration not only with onset in middle life, but also twelve patients whose diabetes began in childhood. The outstanding feature is the extraordinary degree of pathological change found in patients in whom diabetes of long duration had not been well controlled.

MATERIAL

Of the 110 patients, 59 females and 51 males, 79 had been followed clinically for at least six months

before death. Fifteen had been observed at intervals over 15 years, and one patient for over 29 years. Seventy-eight were listed as white Americans. Ten were Hebrews. The remainder included Italian, English, Danish, Irish, Greek, and Syrian persons. All autopsies were done under the direction of Dr. Shields Warren, Department of Pathology, New England Deaconess Hospital.

DURATION OF DIABETES

The diagnosis of diabetes was proved in each instance by the finding of hyperglycemia with glycosuria. When the duration of antecedent polyuria and polydipsia was known, the onset could in some cases be set back one or two years before glycosuria was first found. However, the onset of diabetes was often so insidious that the presumed date of onset must often have followed the actual date by many months or even years. In several cases, diabetes was found when the patient applied for insurance or developed a fatal disease. Among the 19 patients in this series with a record duration of under two years, two died of gangrene. Only one had had a urine examination within five years of the time the diagnosis was made. Fourteen could recall no previous examination. Seven had lost over thirty pounds in weight at least five years before the diagnosis was made. One feels certain that diabetes had been present more than two years in many of these persons. Similar presumed errors in the onset date must have occurred in patients with longer known durations. The date of onset was probably more ac-

TABLE I

DURATION OF LIFE IN 110 DIABETIC SUBJECTS EXPRESSED IN YEARS AND IN PERCENTAGE OF NON-DIABETIC LIFE EXPECTANCY FULFILLED

Age at Onset	Males				Females				Total			
	Number of Cases	Average Duration In Years	Average Life Expectancy Fulfilled	Percent	Number of Cases	Average Duration In Years	Average Life Expectancy Fulfilled	Percent	Number of Cases	Average Duration In Years	Average Life Expectancy Fulfilled	Percent
10-19	5	11.0	20	5	13.4	23	10	12.2	22	12.2	10	8.3
20-29	1	6.0	13	1	4.0	9	2	5.0	11	5.0	2	1.8
30-39	2	4.9	15	3	14.2	38	7	11.7	33	11.7	7	5.3
40-49	13	11.5	45	9	12.5	45	22	11.9	45	11.9	22	16.6
50-59	14	9.9	44	23	11.0	54	37	10.6	50	10.6	37	35.3
60-69	10	11.0	52	13	6.4	30	22	8.4	33	8.4	22	33.3
70-79	6	2.8	35	1	3.3	58	7	3.3	34	3.3	7	1.8
80-89	—	—	—	—	1.8	38	2	1.8	38	1.8	2	0.5
	51	9.5	47	59	10.2	43	110	9.8	44	9.8	44	45.5

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George F. Baker Clinic, New England Deaconess Hospital and Harvard Medical School, Boston, Mass.

curate in the younger patients, whose disease usually begins in an explosive manner.

Table number 1 shows the average duration of life and life expectancy fulfilled for the various age groups. The males lived an average of 9.5 years, the females 10.2 years. The average for the whole group was 9.8 years. In nineteen, the known duration was under two years. Twenty-five lived with diabetes for 15 years or more and nine for over 20 years. The longest duration was a male, who developed diabetes at 47 years. He died at 82 of a myocardial infarct after 34.5 years of diabetes. The average duration of 651 patients in this clinic dying in the Charles H. Best era (January 1944 to May 1946) (2) was 14.1 years. This is 4.3 years longer than the duration of 9.8 years in this series. However, the former group included also patients dying at home. These 110 patients died in the hospital, many being emergencies.

The percentage of long duration cases autopsied at this hospital has increased. In the series of Warren (3) of 527 diabetics autopsied from 1923 to 1938, 12% were over 15 years duration. In our group, 23% were over 15 years.

As shown in Table number 1, the life expectancy fulfilled after diabetes had developed was only 44% for the group as a whole. These life expectancy figures are for the general population and based on Metropolitan Life Insurance Company statistics (4). Eight patients actually exceeded their expectancy. One patient developed diabetes at 60 years; he lived 24 years more, or 162% of his life expectancy. The fulfillment at the various age levels is more important. Thus, the ten patients in table number 1, with onset of diabetes in the second decade lived 12.2 years, longer than any other age group. However, they lived only 22% as long as they would have been expected to live if

they did not have diabetes. The longest duration for a childhood case was 20.9 years (case number 3761, table no. 2) who lived only 34% of her life expectancy. In contrast to the younger group, the patients with onset in the sixth and seventh decades did not live as long in actual years. However, they fulfilled a much greater proportion of their life expectancy, namely 50 and 53%. This is an indication of the greater severity of diabetes among the young. Hanssen (5) made a careful survey of diabetes in Bergen, Norway. He found a similar high mortality among the juvenile cases. In males under 30 years, the mortality was 8.8 times the expected number; in females 6.2 times. This was considerably higher than in the older age groups.

One of the most striking facts elicited in this series is the severity of the vascular pathology found in the younger patients dying with diabetes of long duration. At autopsy, these patients showed severe premature arteriosclerosis with coronary occlusion, degenerative renal sclerosis, and even gangrene. Table number II in order of duration lists those 12 patients with onset of diabetes before thirty years of age. The first five all died within six years of the onset of the disease. They showed essentially no arteriosclerosis. The last seven lived for 14.2 to 20.9 years after onset. They all exhibited severe vascular degeneration.

In the first five patients, with durations of six years or less, no significant degenerative disease was found at postmortem examination. They died before 32 years of age of coma or infection and none showed significant coronary or renal arteriosclerosis. None had hypertension. These are the expected normal findings in non-diabetic persons of 30 years or less.

There is a marked contrast between these findings

TABLE II

Clinical and Pathological findings in twelve patients whose diabetes began under thirty years of age

Case Number	Sex	Age Onset Years	Age Death Years	Duration Years	History of Coma	Hypertension	Retinitis	Coronary Arteries	Nephritis	Principal Cause of Death
22,682	F	19	19	0.2	Yes	No	—	Normal	None	Coma
23,935	M	18	19	1.6	Yes	No	No	Normal	None	Coma
19,972	F	27	31	4.0	No	No	—	Normal	Pyelo., Mild	Hepatitis
21,585	M	11	16	5.5	No	No	—	Normal	None	Sepsis, TBC
16,099	M	22	28	6.0	No	No	No	Normal	None	Appendicitis
7,695	F	18	32	14.5	No	Yes	Diabetic	Occluded	Glomerulo-	Glomerulonephritis
9,500	M	13	27	14.7	Yes	Yes	Proliferans	Occluded	Pyelo., Intercapillary	Pyelonephritis
9,111	F	11	26	15.0	Yes	Yes	—	Narrowed	Arteriolarsclerotic	Arteriolarsclerotic Nephritis
8,405	M	10	25	15.4	Yes	Yes	Proliferans	Narrowed	Intercapillary, Pyelo.,	Intercapillary Nephritis; After Sympathectomy
6,884	F	12	29	16.5	Yes	Yes	Diabetic	Sclerosis Present	Healed Pyelo.,	Hypoglycemia
6,346	M	12	30	17.7	Yes	Yes	Proliferans	Occluded	Intercapillary Pyelo.,	Intercapillary Nephritis After Sympathectomy
3,761	F	10	30	20.9	No	Yes	Proliferans	Narrowed	Arteriolarsclerotic	Arteriolarsclerotic Nephritis

and those present in the seven young patients all dying before 33 years of age with diabetes of 14.5 years or more duration. Three of the latter group had coronary occlusions; in three others the coronary arteries were significantly narrowed by atheromatous plaques. All had serious kidney damage, and six of the seven died principally of renal disease. Intercapillary glomerulosclerosis accounted for two deaths. In these the typical ball shaped masses of hyaline material in the glomeruli were present. Pyelonephritis, nephrosclerosis, and chronic glomerulosclerosis accounted for four deaths. All seven patients had hypertension. Four had retinitis proliferans, a fifth had diabetic retinitis. Tolstoi (6) has suggested that diabetes might be another manifestation of a generalized vascular disease rather than a cause. If this were so, one would expect to find vascular disease in short duration juvenile cases. However, we found significant changes only in the cases of long duration.

In each of these seven long duration diabetic patients, the course of the disease had apparently been benign for the first five or ten years. It is true that coma had occurred in five of the seven and indeed repeatedly in cases number 9500, 6884 and 6346. In our experience, those juvenile patients who have had repeated attacks of coma show by far the highest incidence of visibly calcified vessels by X-ray and other stigmata of degenerative disease.

These autopsied patients are not characteristic of all juvenile diabetic subjects. It is true that in a considerable proportion of the twenty-year cases with onset in youth, arteriosclerosis albuminuria and retinitis are found (2). Dolger (7) stated that of 200 young patients with long duration of diabetes "not one escaped retinal hemorrhages, albuminuria, and/or hypertension in varying degree. Every diabetic would seem at present to be doomed to the inexorable development of vascular damage despite the benefit

of insulin in prolonging life." However, in the group of 300 juvenile diabetics who have survived 20 years of diabetes studied by White (7a), 15 have been proved completely free of degenerative disease. These patients as of June 1947 have been examined especially in regard to blood pressure, renal function, capillary fragility and electrocardiogram, as well as intravenous pyelograms, X-rays of the legs and of the aorta for arteriosclerosis and finally by an ophthalmologist. These patients have demonstrated that even in youthful diabetics vascular and renal complications may be prevented for at least 20 years.

Since diabetes markedly accelerates degenerative processes, vascular complications are more common in long duration cases. This was shown above in Table II for the younger patients where degenerative disease occurred exclusively in the long duration patients. There was an appreciable increase with duration of diabetes in the incidence of complications when the group as a whole was considered. Table III shows the percentage of patients with various complications divided into those with a duration under five years and those with a duration of eleven years or more. The first, or short duration group, contained 32 patients; the eleven year or more group contained 53 patients. The two groups are similar in regard to sex distribution and age at death as well as severity of diabetes as measured by insulin dosage and average blood sugars. Both groups were found to have a striking number of complications. However, the longer duration patients showed a 10% to 27% greater incidence of cardiovascular deaths, degenerative renal and pancreatic lesions, hypertension, and absent dorsalis pedis pulsations. This cannot be explained on the basis of age at death, since the long duration cases lived only an average of 1.0 year longer than the short duration cases.

Insulin has enabled persons with diabetes to live long enough to develop degenerative complications. Thus the mortality has become greater in those with long durations of the disease. This is shown in Table 40 of the 8th Edition of the Treatment of Diabetes Mellitus (2). The mortality for all patients attending this clinic in the first five years of the disease in the 1944 to 1946 period was only 15%. It increased to over 20% in each five year group of over 10 years duration. This represents a reversal of the experience before insulin. Hanssen (5) found a similar rise in mortality with duration of the disease. However, he noted that the mortality rate in the younger patients actually decreased with duration. His mortality rates were low in juvenile diabetic subjects of over 10 years duration. He did not encounter such patients developing degenerative diseases. Likewise Lisa and Hart (8) found no evidence of significant arteriosclerosis in eight juvenile diabetics. However, none of their eight patients had had diabetes over 10 years. It is notable that some pediatric textbooks do not emphasize the severe vascular disease that appears in diabetic children, as described by Eisele (9) and Rosenbusch (10).

TABLE III

Comparison of Patients with Diabetes under Five Years with those over Eleven Years

	Duration of Diabetes	
	0 to 5 years	11 years or more
Number of patients	32	53
Female	16	24
Sex — Male	16	29
Ave. Age at Death	60.6 yrs	61.6 yrs.
Ave. Age at onset	56.7 yrs.	46.0 yrs.
Onset under 30 yrs.	5 (16%)	7 (13%)
Insulin over 20 U.	14 (52%)	29 (56%)
Ave. Bld. Sugar 150 mgm % or over	13 (68%)	30 (68%)
Death primarily cardiovascular	17 (53%)	36 (68%)
Severe Coronary sclerosis	19 (61%)	40 (75%)
Degenerative renal lesions	15 (47%)	30 (57%)
Degenerative pancreatic islet lesions	21 (66%)	42 (81%)
Hypertension	16 (50%)	36 (68%)
Absent Dorsalis pedis pulsations	8 (25%)	24 (46%)

Percentages are adjusted for charts lacking necessary data

CAUSES OF DEATH

The autopsy protocols were examined and correlated with the clinical records. A principal, rather than a precipitating, cause of death was assigned to each case. For example, patients dying with a coronary occlusion after an amputation for gangrene were classed as gangrene deaths. In numerous autopsies, a striking number of severe lesions were found. On pathological grounds alone, these patients could have died from several causes.

In Table IV, the pathological data of the 110 autopsies are summarized. The first column lists the occurrence of the principal causes of death. Conditions present as a complication, but not as a principal cause of death are listed in the second column. For example,

TABLE IV

Summary of Pathological Findings in Diabetic Patients

	Principal Cause of Death	Also Present
1. Diabetes		
Hypoglycemia	1	2
Coma	4	1
Total	5	
2. Vascular Degenerative Disease		
Myocardial infarct	29	43
Myocardial failure	9	39
Cerebral hemorrhage or thrombosis	5	3
Mesenteric infarct	2	0
Gangrene of extremity	10	3
Nephritis (excluding pyelonephritis)		
Intercapillary	2	3
Arteriosclerotic	6	29
Glomerular	1	2
Pulmonary embolus	1	9
Arteriosclerosis, all degrees	0	108
Total	65	
3. Infections		
Pyelonephritis, chronic	3	18
Lobar pneumonia	2	1
Abscesses, lungs	2	0
Cholecystitis, acute	2	3
Appendicitis, acute	2	0
Septicemia, pyemia	3	6
Tuberculosis		
Sinuses	1	0
Elsewhere	0	3
Duodenal ulcer perforated	1	3
Hepatitis, acute	1	2
Carbuncle	3	1
Syphilis	0	2
Rheumatic valvular heart disease	0	4
Total	20	
4. Carcinoma		
Total	16	8
5. Miscellaneous		
Hemochromatosis	2	1
Fracture, left femur	1	0
Periarthritis nodosa	1	0
Clrthrosis	0	12
Pathological changes in pancreatic islets	0	87
Total	4	
Total Deaths	110	

8 patients died of cardiac failure; in 39 others failure was present at time of death, but was not the principal cause of death.

Of the 110 patients, five died of disease directly attributable to diabetes itself (coma 4, hypoglycemia 1). Another group of 20 patients died of disease not related to diabetes mellitus (cancer 16 and miscellaneous 4). Of the remaining 85 patients (65 dying with vascular degenerative disease and 20 with infections) diabetes was undoubtedly a critical factor. Thus in 90 subjects or 82% of this series, diabetes was either directly or indirectly responsible for death. Before the advent of insulin, 67% of the patients of this clinic (2) died within the first five years of their disease, principally of diabetic coma. Now that acidosis can be prevented, only 16% of the patients die within the first five years of their disease. However, having passed the Scylla of coma by means of insulin diabetic persons eventually founder upon the Charibdis of premature degenerative disease.

Because diabetes alone usually does not cause death, the word "diabetes" is often omitted from death certificates. Physicians are interested in the precipitating cause of death; this often is a disease which has been greatly aggravated or accelerated by the diabetes. However, if the diabetes seems not to be an immediate factor at the time of death, it may not even be entered on the death certificate. In this series there were nineteen patients who took no insulin before their final illness. Some had had diabetes as long as 16 years. The omission of this type of patient from mortality figures is very common and tends to minimize the importance and prevalence of diabetes. Joslin and Lombard (11) found the word "diabetes" omitted from death certificates of about one-third of 744 diabetic persons. Lundberg, quoted by Hanssen (12), stated that "It is probable that the time will come when it will be quite impossible to employ mortality figures for estimating the frequency of diabetes in the population."

DIABETIC COMA

From 1914 to 1922 coma accounted for 42% of the diabetic deaths in the experience of this clinic (2). With the advent of insulin, the coma death rate fell precipitously. Now only 3% of the deaths are associated with coma. The rare complications of diabetes are not curable; coma is, and such deaths are usually avoidable. In this series four patients died following diabetic acidosis. Three of these deaths perhaps could have been avoided if early and adequate treatment had been given. The fourth died with a coronary occlusion after apparent recovery from acidosis. A summary of these cases follows:

Case number 5233. A 67 year old female with diabetes of 22 years duration was transferred from another hospital after unconsciousness of 12 hours and anuria of several hours. Respirations were shallow, 30 minutes. Blood pressure was systolic 40 mm. Hg.; diastolic 0 mm. Hg. Blood sugar was 687 mgm%, blood carbon dioxide 10 ml. mol. per liter. She was given 400 units of insulin in 2 hours and intravenous normal saline solution. Anuria persisted and she died nine hours after admission. At autopsy, a

small focus of bronchopneumonia; petechial hemorrhages in brain, epicardium and pleurae; generalized arteriosclerosis; considerable glycogen in the cytoplasm of the hepatic cells were found. This patient is unusual because of the long duration of diabetes. She had not been seen for 18 years before final admission. No history was elicited from the family of previous serious difficulties with her diabetes.

Case number 23935. A 19 year old male with diabetes of 1.6 years duration broke his insulin syringe three days before admission. He was transferred from another hospital after unconsciousness of about 12 hours. During the preceding 24 hours he had received at least 500 grams of glucose. Temperature was 104° rectally, blood sugar 678 mgm.% and blood carbon dioxide 10.5 ml. mol. per liter. There was no acetone or diacetic acid in the urine. The blood contained a negligible amount of acetone bodies. After 220 units of insulin and intravenous salt solution, blood sugar fell to 220 mgm.% and blood carbon dioxide rose to 18 ml. mol. per liter. The patient died nine and one-half hours after admission without regaining consciousness. At autopsy, pulmonary congestion and edema, arteriosclerosis of aorta and liberal amounts of fat and glycogen in the liver were found.

This patient has been discussed in a case report by Root and Leech (13) as illustrating hyperglycemia stupor.

Case number 22682. A 19 year old female with diabetes of two months, never treated, was transferred from another hospital after a respiratory infection of four days and unconsciousness for most of 36 hours. On examination, blood pressure was 72 mm. Hg, systolic and 40 mm. Hg, diastolic; there was unconsciousness and severe pharyngitis. Blood sugar was 534 mgm.% and carbon dioxide 5 ml. mol. per liter. She was given 200 units of insulin and intravenous saline solution. Four hours after admission blood sugar was 165 mgm.%. She excreted only 20 cc. of urine and died six hours after admission.

Autopsy showed purulent sinusitis of the sphenoid and ethmoid, pulmonary congestion, early bronchopneumonia, atherosclerosis of aorta and glycogen in the hepatic cells.

This patient had a respiratory infection which induced coma in previously untreated diabetes.

Case number 5792. A 59 year old female with diabetes of 24 years duration complained of nausea, vomiting, and a "congestion" in the chest for two days before entry. Examination revealed a fully conscious patient with slight Kussmaul type breathing. Blood pressure was 100 mm. Hg, systolic and 60 mm. Hg, diastolic; blood sugar 512 mgm.% and blood carbon dioxide 9 ml. mol. per liter. Eighteen hours after admission, after 202 units of insulin and 2000 cc. of normal saline intravenously, blood sugar was 57 mgm.% and carbon dioxide 18 ml. mol. per liter. A later blood sugar was 244 mgm.%. She died 36 hours after admission in congestive heart failure.

At autopsy, coronary arteriosclerosis with a recent myocardial infarct, bilateral pleural effusion, islet cell adenoma of pancreas, and glycogen infiltration of liver were found.

This patient died in congestive heart failure following a recent myocardial infarct. She had chemically recovered from acidosis before death. Since acidosis and its treatment may have played a role in causing death this case is classed as due to acidosis.

HYPOGLYCEMIA

Most persons with diabetes fear insulin reactions more than the less dramatic, remote, degenerative complications, which are more apt to be death-dealing. Hypoglycemia is an ever-present challenge to their security. It often comes on with little warning, caus-

ing severe embarrassment. Although it may have severe deleterious effects, fortunately it is rarely fatal.

In this series, only one death was definitely caused by insulin hypoglycemia.

Case number 6834. A 29 year old female with diabetes of 16.5 years duration had a history of poor control with many attacks of acidosis and insulin reactions. She had been hospitalized for diabetic coma over ten times. While undergoing treatment in this hospital for peripheral neuritis, she developed a severe insulin reaction. It was suspected that she herself had taken 800 or 1600 units of insulin. She failed to regain consciousness and expired 31 days later, having been transferred to the Boston Psychopathic Hospital.

At autopsy, Dr. Paul Yakovlev (14) found "the meninges were thickened, opalescent, and congested . . . There were widespread degenerative, non-inflammatory, necrotizing lesions in almost every part of the brain. These consisted of degeneration and loss of nerve cells, marked increase in the nuclei of the microglia and protoplasmic glia . . . The silver impregnations showed presence of numerous argentaffine plaques exclusively in the cerebral cortex and striatum." Elsewhere healed pyelonephritis, coronary sclerosis, acute bronchitis, and hepatomegaly were found.

In a second case, hypoglycemia may have been an important factor.

Case number 25,539. A 63 year old female with diabetes of 7.9 years was admitted in an unconscious state. Blood sugar was 26 mgm.%. She regained consciousness five minutes after glucose was injected intravenously. She expired suddenly 20 hours later, shortly after a blood sugar (98 mgm.%) had been taken. At autopsy no cause of death was found. Unfortunately no head examination was permitted. In this case, the clinical diagnosis of cerebral hemorrhage has been accepted as correct.

The findings in death due to hypoglycemia have been described by Bowen and Beck (15), Root and Lawrence (16), et al. (17).

Hypoglycemia attacks are particularly common in sick diabetic subjects. The disease is apt to be out of control at this time and large doses of insulin used. Whether hypoglycemia is a factor in precipitating vascular occlusions in brain, heart or legs can not be answered from this material. Root and Styron (18) studied 205 insulin reactions in this clinic. No vascular accidents or attacks of angina pectoris were observed. Erstene and Altschule (19) found hypoglycemia was accompanied by increased cardiac work. Root concluded that hypoglycemia may have serious effects on already damaged heart in some instances. Harrison and Finks (20) described relative or actual hypoglycemia in non-diabetic subjects which precipitated attacks of angina pectoris, cardiac arrhythmias and hypertensive encephalopathy.

An autopsy is of extreme importance in all deaths believed due to an insulin reaction. This is illustrated in the case cited immediately above (number 27,539). Physicians and patients' families naturally tend to make this diagnosis in any illness involving unconsciousness in a person with diabetes. In the following two cases, simple hypoglycemia had been incriminated as the cause of death until the autopsies revealed other conditions.

Case number 25201. A 43 year old male with diabetes of six months duration died suddenly at home. A blood sugar

taken shortly after death was 52 mgm.%. At autopsy a recent coronary occlusion was found.

Case number 5570. A 79 year old male with diabetes of 15.3 years duration became unconscious at home. A blood sugar was 557 mgm.%. He was then given 140 units of insulin. On admission to this hospital the blood sugar was 37 mgm.%. At autopsy, a recent cerebral hemorrhage was found.

ARTERIOSCLEROTIC HEART DISEASE

Arteriosclerotic heart disease was the most important single cause of death. Twenty-nine patients died of myocardial infarction. Nine others died primarily of congestive heart failure, due to arteriosclerotic heart disease. Thus 38 patients (36%) died of degenerative heart disease. The proportion of cardiac deaths among all patients attending this clinic has risen from 6% to 45% in the last 25 years largely at the expense of coma deaths. Robbins and Tucker (21) in 1944 found that coronary occlusion was 2.5 times as common a cause of death in their series of diabetic as in non-diabetic subjects.

The total incidence of coronary atherosclerosis in these patients is even more remarkable. Of 110 patients, examination of the coronary arteries was permitted in 106 instances. The arteriosclerotic lesions were classified after the method of Root, Bland, et al. (22) as follows: Class I -- no macroscopic lesion of the coronary arteries -- 11 patients (10%); Class II -- sclerosis without significant narrowing of the coronary arteries -- 22 patients (21%); Class III -- significant narrowing of coronary arteries without actual occlusion -- 36 patients (34%); Class IV -- occlusion of coronary artery -- 36 patients (34%). In Table V these percentages are compared with those of Root, Bland, et al.

TABLE V

Degree of Coronary Sclerosis in Diabetics and non-diabetics

	Class I	Class II	Class III	Class IV
106 cases diabetes (this series)	10%	21%	34%	34%
249 cases diabetes (Root, Bland et al.)	26%	23%	29%	22%
3460 cases not diabetes (Root, Bland et al.)	52%	27%	14%	6%

The two diabetic series show an incidence of 34% and 32% respectively with coronary occlusions (Class IV). This is over five times the occurrence of this lesion in the non-diabetic group (6%). Similarly only 10% of the present series had no macroscopic sclerosis of the coronary arteries (Class I), whereas Root, Bland, et al. found over half (52%) of the non-diabetics with normal coronary arteries.

Lisa, Magiday et al. (23) found coronary occlusions in 30% of 138 diabetic autopsies. This compared with an incidence of 22% in their adjusted non-diabetic control series. They concluded that arterio-

sclerosis appeared earlier in persons with diabetes. Hansen (5) however reported only six of 108 deaths due to arteriosclerotic heart disease with 11 other patients showing some coronary sclerosis.

The figures above in Table V on coronary sclerosis give an indication of the prevalence of arteriosclerosis in this series. Thus 95 or 89% of 106 patients showed arteriosclerosis of the coronary arteries. In four patients included in the 106 patients in Table V, only abdominal examination was permitted. All four showed marked sclerosis of the aorta. Of the remaining 11 patients without macroscopic sclerosis of the coronary arteries or aorta, all but two showed microscopic degeneration of the coronary arteries or atherosclerosis elsewhere. Therefore, of 110 patients, 108 showed some degree of arteriosclerosis. The two showing none were case number 23,935 and 19,972 in Table II, both young persons dying within five years of the onset of diabetes.

However, atherosclerosis of minimal degrees may be of little clinical significance. Above it was shown that 72 patients either had coronary occlusions or marked narrowing of the arteries by atherosclerosis. Of the remaining 38 patients with little or no coronary sclerosis, 13 had either nephrosclerosis or absence of one or both dorsalis pedis pulsation. Thus 85 (77%) of 110 diabetic patients showed evidence of atherosclerosis of clinical importance.

The severe arteriosclerosis found in the seven young diabetics of long duration has been shown above in Table II. These seven patients were of an age at which degenerative vascular disease is very uncommon in non-diabetics. However, three aged 28, 30 and 32 years had coronary occlusions and three others showed severe coronary sclerosis without actual occlusions. The occurrence of coronary occlusions in young diabetics has been described by Warren (3) and Cullinan and Graham (24).

CEREBROVASCULAR ACCIDENTS

Five patients died principally of cerebrovascular accidents; this was an incidental finding in three others. It is of interest that all eight were suspected initially to be hypoglycemic coma. In only one, however, was there a definite relationship. This was case number 27,539 discussed under hypoglycemia. Jordan and Watters (25) in 1933 reviewed 70 cases of cerebrovascular accidents in this clinic. They concluded that such accidents did not differ from similar occurrences in non-diabetic subjects.

PULMONARY EMBOLUS

White (26) wrote that pulmonary embolism is variously recorded as being found in 8 to 12 per cent of routine autopsies. Therefore the incidence of 10 (9%) in this series is not remarkable. Of the ten patients with pulmonary emboli, in only one was this the principal cause of death, but it was the immediate and precipitating cause in five others. Four deaths followed surgical operations. In five of the ten subjects, venous or right auricular thrombi were identified.

PERIPHERAL VASCULAR DISEASE

The high incidence of arteriosclerosis obliterans in diabetes mellitus as well as its high frequency among long duration cases, and its apparent postponement by early insulin therapy were illustrated in this material.

Of 110 patients, 45 (41%) showed absence of pulsations of one or both dorsalis pedis arteries. Thus over two-fifths of the patients had evidence presumably of significant peripheral vascular disease; gangrene probably could have occurred in any of them within a few years if they had not died of other causes. Dry and Hines (27) found peripheral arterial insufficiency eleven times as common in diabetics as among non-diabetic patients and that it tended to occur at an earlier age.

The absence of dorsalis pedis pulsations was noted more frequently among the long duration patients. Thus only eight (25%) of the 32 persons with a duration of diabetes of five years or less showed absent pulsations; whereas twelve (48%) of those 25 persons with diabetes 15 years or longer had no dorsalis pedis pulsations. In Naide's (28) series of 100 patients with a duration of ten years or more, 30% had one or more absent pulsations.

Peripheral vascular disease was more common among those who had delayed the use of insulin. Of 45 patients with absent dorsalis pedis pulsations, 40 required insulin for proper control of their diabetes. They did not begin taking insulin until an average of 4.7 years after onset of their disease. Of the 65 patients with normal dorsalis pedis pulsations, 60 required insulin. They began insulin much earlier, at an average of 1.7 years after onset of diabetes. This was three years earlier than those with absent pulsations. This finding suggests that early use of insulin is instrumental in avoiding peripheral vascular complications. In Joslin, Root, et. al. (2) a similar finding is recorded. Two hundred and thirty patients who underwent amputations in the years 1939-1942 took no insulin for an average of 6.9 years after the onset of the diabetes.

In the experience of this clinic (2), the percentage of gangrene deaths rose from 4.2% to 8.1% with the advent of insulin. Until recently most patients with gangrene died of infection. Now gangrene deaths have fallen to only 3.1% due to the value of chemotherapy and antibiotics in controlling infection. Most deaths due to gangrene now are precipitated by vascular accidents elsewhere in the body. In this series, of ten patients who died principally of gangrene, the immediate cause of death in all was arteriosclerosis elsewhere. Of these, five died in cardiac failure due to arteriosclerotic heart disease, three of coronary occlusions, and two of pulmonary emboli. Seven of these deaths occurred after amputation; in the other three amputation had been considered but had not been done because of the condition of the patient.

Three patients, in addition to the ten above had gangrene at the time of death as a secondary finding.

These died respectively of carcinoma of the liver, gangrene of the mesentery, and following sympathectomy in a patient with pyelonephritis and intercapillary glomerulosclerosis. This last patient, Case 6346, Table II, was the youngest in whom gangrene occurred, being 30 years of age at death.

Allen, Barker, and Hines (29) state that "the factors which produce arteriosclerosis obliterans of the lower extremities are likely to lead to similar lesions in other parts of the body . . . Within a few years arterial lesions frequently appear in one of the vital organs." This is illustrated in this series by the eight patients who finally came to autopsy and who had had amputations for gangrene 6 months to 3.5 years previously. One died of infection but seven of the eight died of vascular accidents. Three of these also had further gangrene at death.

RENAL DISEASE

The kidney has become a particularly vulnerable site of fatal disease in diabetes mellitus. This has followed in the wake of degenerative vascular disease. Fifty-seven (52%) of 110 autopsy protocols recorded well-marked nephritis. In 26 patients, two or more forms of renal disease were present. In 12 chronic nephritis was the cause of death.

The commonest form of nephritis was arteriolar, occurring in 35 cases. This accompanied the high incidence of hypertension (59%). Six patients died in uremia due to this disease.

Persons with diabetes mellitus are peculiarly susceptible to pyelonephritis, at present perhaps the most important single infection (Sharkley and Root (29a); Bowen and Kutzman (29b)). Harrison and Bailey (30) reported bacilluria in 27 of 50 unselected diabetic subjects. Robbins and Tucker (21) reported that 21 of their 301 diabetic subjects died of pyelonephritis. This was 4.5 times as common a cause of death as in their adjusted control non-diabetic group.

In our series, 13 patients had active pyelonephritis at autopsy; in three of these, this was the principal cause of death. No instances of necrotizing pyelonephritis (31, 32) were present. In eight other patients healed pyelonephritis was present. This indicates that diabetics often can heal this lesion.

Intercapillary glomerulosclerosis has been widely reported since Kimmelstiel and Wilson (33) in 1936 first described "a striking hyaline thickening of the intercapillary connective tissue of the glomerulus." Horn and Smetana (34) and Goodoff (35) in large series found this lesion in advanced form only in diabetes mellitus. Laipply, Eitzen, and Dutra (36) considered this lesion as more specific of diabetes than hyalinization of the islets of Langerhans.

The autopsy protocols of 15 (14%) of 110 patients recorded the presence of well marked intercapillary glomerulosclerosis. Laipply, Eitzen and Dutra (36) found some degree of change in as high as 64% but a severe degree occurred in only 11% of their series. Of

15 subjects 12 were over 50 years of age at death. They were principally patients with diabetes of long duration. Only 2 of the 15 had had diabetes under 5 years. Goodoff (35) also found the incidence to increase with duration.

Because of the frequent association of intercapillary glomerulosclerosis with other forms of renal disease, it has been difficult to assess its relative importance. Of the 15 patients with this lesion, six had arteriolar nephrosclerosis, four pyelonephritis in addition to the intercapillary lesions. Horn and Smetana (34) and Laipply, Eitzen, et al. (36), called attention to the high incidence of nephrosclerosis in such patients.

A patient with severe intercapillary glomerulosclerosis may show a typical complete renal syndrome of nephrosis and later renal failure as described by Derow, Altschule, et al. (38) and by Newberger and Peters (39). However, such a typical course has proven to be the exception in our experience. It is true that 14 of the 15 subjects had hypertension and albuminuria. However, only three developed a nephrotic phase with hypoproteinemia and edema. In two of these three, the predominating renal lesion was pyelonephritis. Siegal and Allen (40) and Laipply, Eitzen et al. (36) also found the complete renal syndrome often absent. Bell (41) concluded that intercapillary glomerulosclerosis could not be diagnosed with certainty during life.

The seriousness of renal disease in young diabetic subjects is indicated by the fact that six of the seven juvenile long duration patients died of nephritis. The seventh patient had had a right nephrectomy three years before death for pyelonephritis. These patients all ran essentially similar clinical course whether the underlying predominating renal lesions were intercapillary glomerulosclerosis, pyelonephritis, nephrosclerosis or glomerulonephritis.

Rosenbusch (10) recently reported glomerulosclerosis as a late complication among 80 subjects whose diabetes began in childhood. Typically the patients showed albuminuria with benign nephrosis in the early stages and later malignant hypertension, retinitis and cataracts. Many of his patients at autopsy showed more than one form of nephritis.

Clinically many instances of chronic nephritis in young diabetics have been observed in this hospital in addition to the six listed in Table II. In these patients there has usually been a history of irregularity of diet. During the first few years of the disease diet has been carefully observed and the urine kept nearly sugar free. Then, however, these young patients, especially during adolescence, have given up careful diet and have no longer attempted to keep blood and urine tests normal. In most, recurrent diabetic acidosis has occurred. During the first few months of the renal disease, edema and albuminuria associated with a definite nephrotic syndrome may appear. However, the nephrotic phase often is absent. Invariably after a period of months or a year or two, the stage of

nitrogen retention occurs. When this becomes established there usually appears retinitis and hypertension progressing to blindness, deficient peripheral vascular disease, angina pectoris, or coronary occlusion. The course is rapidly downward with death in a year or two.

The difficulties involved in etiological diagnosis in the younger patients are illustrated by Case 9500, Table II, where a typical course justifying the diagnosis of intercapillary glomerulosis had been followed. After about ten years of diabetes he began to show albuminuria, then edema, and finally hypertension. His retinitis began with hemorrhages and later entered the proliferative stage. He had had coma on more than one occasion. The final death from coronary occlusion occurred after a period of some months during which nitrogen retention, edema and uremic symptoms had been present. The kidney lesions were chiefly those of pyelonephritis with however some typical areas of intercapillary glomerulosclerosis. Similarly Case 3761 (Table II) who died of arteriolar sclerotic nephritis without significant intercapillary changes exhibited a nephrotic syndrome and later uremia. On the other hand, only one of the two patients who did die of intercapillary glomerulosclerosis had clinical nephrosis.

PANCREATIC FINDINGS

Abnormalities of the pancreas were noted in 87 autopsies (79%). These changes consisted of hyalinization of the islets of Langerhans, diminished number of islets, or interstitial fibrosis. This is in addition to five cancers of the pancreas. In other large series of diabetic autopsies, changes in the pancreas have likewise been found in about 80%. Thus Warren at this hospital (2) found 76% in 527 autopsies; Dry and Tessmer (42) 85% of 201 cases; and Gibb and Logan (43) 77% of 142 cases.

Pancreatic changes were more frequent in the long duration and older cases. The above abnormalities were present in only 66% of those with a duration of five years or less; in those of longer duration, i. e. six years or more, 86% showed changes. In regard to age at death, among those 20 patients dying at 50 or less years of age, 65% showed pancreatic changes. Those subjects 51 years or more at death showed changes in 82% of the cases. The data showed no relationship between changes in the pancreas and the incidence of hypertension; kidney, heart, or peripheral vascular diseases; nor to poor control and prolonged hyperglycemia. Lukens and Dohan (44) have recently produced diabetes in cats by maintaining prolonged hyperglycemia.

HYPERTENSION

Sixty-five (59%) of 110 patients had blood pressure over 150 mm. Hg. systolic and 90 mm. diastolic which were used as the lower limits of normal (26). A high rate of hypertension among diabetic persons has been often recorded. Root and Sharkey (45) in 1936 reported hypertension in 54% of 175 diabetic deaths. Edeiken (46) found that 38% of 100 living persons with diabetes over 10 years had high blood

pressure. Haussen (5) in Norway found a similar high percentage among persons over 50 years of age. However, he found that its occurrence in younger patients was rare. Our experience is in striking contrast to this, as is illustrated in Table II. Among those twelve persons whose diabetes began before 30 years of age none had hypertension where the duration was under 10 years. However, all seven of the long duration cases had well-marked high blood pressure, the oldest being only 32 years of age at death.

This frequency of hypertension (59%) accompanied in this series the high incidence of significant arteriosclerosis (68%) and arteriolarsclerotic nephritis (23%). Thirty-nine per cent of the hypertensive subjects showed coronary occlusions, while only 24% of the non-hypertensive group had coronary occlusions. Ten of 13 persons with gangrene as well as 30 of 45 persons with absent dorsalis pedis pulsations had hypertension.

TABLE VI

The Incidence of Hypertension in Relation to Duration of Diabetes

Duration in Years	Total Patients	Patients with Hypertension	Percentage With Hypertension
0 to 5	35	16	46%
6 to 10	24	15	63%
11 to 15	25	14	56%
16 and over	26	20	77%
	110 patients	65 patients	59%

A definitely higher incidence of hypertension was found among those persons who had diabetes the longest. Table VI shows that the incidence of high blood pressure was 46% in those dying after diabetes of five years or less. This is a high figure, but in those persons with diabetes of 15 years or more, the occurrence of hypertension was 77%.

INFECTION

Of 110 patients, twenty died primarily of infections. Five died with peritoneal infection and rupture of an abdominal viscus (appendix 2, gall bladder 2, duodenum 1). Two of these five died after surgical procedures. Carbuncles, non-tuberculous pulmonary infection, septicemia, and pyemia accounted for nine deaths. One cannot say that diabetes was responsible for these deaths. However, it probably was a severe aggravating factor in each case. The low resistance to infection and the decreased carbohydrate tolerance during infection is discussed by Joslin, Root, et al.(2).

Acute hepatitis was the cause of death in a 31 year old woman Case 19,972, Table II, who died four months after a successfully terminated pregnancy. Two

other patients showed mild hepatitis at autopsy as an incidental finding. Vannjätt (47) considered a certain tendency toward hepatitis on the part of diabetic subjects to be probable. He and Droller (48) described epidemics of acute hepatitis occurring in diabetic clinics. Twelve patients showed mild cirrhosis.

Only one patient died of tuberculosis. This was a 16 year old boy (Case 21,585, Table II) with diabetes of 5.5 years duration who developed tuberculosis of the antrum. He died when the process spread to the central nervous system, causing an acute tuberculous meningitis. In five other patients small foci of tuberculosis were present in the lungs, ilium or kidney. None of these had been recognized during life. Persons with diabetes and pulmonary tuberculosis for the most part die in sanatoria and not in a general hospital. Therefore they would not be in a series such as this. At present 2.5% of all our patients die of tuberculosis (2). Richardson and Bowie (49) found nine cases among 100 living diabetic persons. Haussen (5) reported 4.1% of the deaths in his series in Norway as due to tuberculosis. However, Vartiainen (50) in Finland found a very high incidence. Eighteen of 85 patients in the insulin era died of this disease. These statistics all represent a great improvement over Naumyn's mortality of 39% in 1906.

CANCER

Cancer was the cause of death in 16 patients. In 8 other persons small carcinomata were present as incidental findings. Five (21%) of the 24 carcinomata were pancreatic in origin. The unexplained high incidence of carcinoma of the pancreas has been noted previously but the relationship to diabetes is not understood. At this hospital in 1928 McKittrick and Root (51) reported 12 pancreatic among 37 cancers, while Marble (52) found 33 among 256. Elsewhere Dry and Tessmer (42) found 6 in 38 diabetic persons dying of cancer. However, Ellinger and Lansman (53) reported only 2 among 39 malignancies.

Cancer like infections may be considered as an "accident" in the lives of persons with diabetes, usually causing death before the onset of severe degenerative disease. Thirty-four of 75 persons who did not die of cancer or infection had coronary occlusions at autopsy; whereas only 2 of the 34 subjects dying of cancer or infection had coronary occlusions.

TREATMENT

The immediate goals in the treatment of diabetes are the attainment of normal body weight, freedom from acidosis, and absence of characteristic diabetic symptoms. However, the more important object is the prevention of severe vascular degeneration such as occurred in this series. During periods of hospital observation control of the diabetes was sought by the use of insulin and diets providing 150 to 200 and occasionally perhaps to 300 grams carbohydrate with 30 to 50 calories per kilogram of body weight. However, in this group the periods of close observation were brief and the great part of the patient's diabetic life

was spent away from medical observation and evidently in most cases without close supervision. The use of high carbohydrate diets began in 1926. Stolte (54) and many others have advocated a "free" diet particularly for children. Recently the opinion has been expressed often that the use of insulin without rigid dietary restriction is proper therapy. As yet no series of autopsies has appeared indicating that vascular complications are thereby lessened.

The opposing view has been that careful treatment by diet and insulin indicated by normal blood and urine tests would protect the patient against such complications as coma and premature degenerative diseases. (Joslin 2, Ricketts 55). The use of insulin even with slight dietary treatment will protect most patients during the first years. During this time patients may "adapt" to their disease as in Selye's experiments. Selye (56) has shown that an animal is able to adapt to various noxious stimuli for a considerable time without apparent ill effects. In Selye's experiments following the period of adaptation to noxious stimuli an exhaustion phase appeared characterized by degenerative vascular disease. The vascular disease in diabetes may represent this exhaustion phase after a long exposure to the strain of the abnormal carbohydrate metabolism. We believe that efforts to keep the metabolism as nearly normal as possible by the use of insulin and diet may postpone the advent of degenerative disease. It has not been proven that there is any deficiency other than insulin in diabetes. Diabetic subjects die chiefly of vascular disease in legs, heart and kidneys. The importance of diabetes in causing these lesions is often minimized, but death comes much earlier on the average than in non-diabetic patients. This amounts to a few years in aged persons but to several decades in the young. Therefore, to evaluate diabetic therapy properly, no matter how brilliant the immediate results may be, one must wait 15, 20, or even more years in young patients. A further difficulty in assessing diabetic therapy is that it is often impossible to tell the actual degree of day to day control of sugar metabolism by insulin. Most patients when feeling well see a physician only occasionally. Furthermore, individual temperaments and intelligence vary widely.

CONCLUSION

1. The records of 110 diabetic patients examined post-mortem at the New England Deaconess Hospital between 1940 and Jan. 1, 1946 disclosed degenerative vascular complications involving principally the coronary arteries and kidneys as the chief cause of death. In this series are included 10 patients whose diabetes began under 20 years of age and two with onset between 22 and 27.

2. Although the average duration of life of 9.8 years in this series has increased almost fourfold as compared with the series of Naunyn, 1906, and has exceeded the duration of diabetes in other series of autopsied cases from this same hospital, nevertheless, few patients attained normal life expectancy and the

average only fulfilled 44 per cent of the life expectancy for non-diabetic patients of the same age.

3. In five patients whose diabetes began between the ages of 11 years and 27 years, no significant arteriosclerosis was found in the coronary vessels or other arteries, when the duration of the diabetes varied from 0.2 years to 6.0 years. In contrast, seven cases with onset of diabetes between the age of 10 years and 18 years, with duration of diabetes varying from 14 years to 20.9 years, demonstrated marked narrowing or complete occlusion of coronary arteries in addition to arteriosclerotic lesions elsewhere including the kidneys and legs.

4. Diabetes of long duration produces in young patients vascular lesions of all three types. The early evidences may be in the retinal vessels or demonstrable as visible calcification by X-ray in the vessels of the legs. The development of renal failure in the seven youthful cases of long duration was characterized by early edema with an apparently benign nephrotic syndrome including increased blood values for cholesterol and hypoproteinemia. This apparently benign stage within a period of one or two years was followed by hypertension of a malignant type associated with eye ground changes and eventually nitrogen retention. This course has occurred with any of three different predominating renal lesions or with combinations, that is, arteriolar nephrosclerosis, intercapillary glomerulosclerosis, or pyelonephritis.

5. The striking feature of the histories of the young patients subsequently developing vascular disease and a renal failure was that during the first few years of the disease the diabetes was well controlled by careful dietary treatment and insulin. However, during the last eight or ten years of the disease usually diabetes was no longer under control owing to laxity in following diet, periods of acidosis, and intercurrent infection. In the etiology of vascular disease associated with diabetes, the first factor to be considered is the essential deficiency of a single hormone, insulin. A dietary or nutritional factor in some way related to the lack of balance between the supply of the specific hormone insulin and the normal utilization of a proper diet is clearly indicated. Diabetic coma, indicating the maximal degree of the uncontrolled diabetes, had been present in five of the seven youthful cases with severe arteriosclerosis.

6. Some degree of arteriosclerosis was present in 99 per cent and was of clinical significance in 77 per cent of the 110 patients. Severe coronary arteriosclerosis occurred in 68 per cent of the cases and peripheral vascular disease in 41 per cent. Degenerative changes in the Islands of Langerhans in the pancreas were present in 79 per cent and chronic renal disease was present in 52 per cent of the series as a whole.

7. The gradual development of vascular lesions in youthful diabetic patients needs study by various functional tests of renal, cardiac and vascular phenomena as well as by X-ray examinations. Youthful patients must be followed for 15 years or more if any con-

clusions are to be drawn as to the presence or absence of degenerative vascular lesions and particularly if conclusions are to be drawn with regard to the effect of different types of treatment. In the present series no cases are found in whom long periods of carefully controlled diabetes were associated with the development of premature vascular disease in young people. In middle aged and older patients in whom mild dia-

betes had long been controlled by dietary treatment, severe vascular lesions seemed to be postponed. In young patients the postponement of premature vascular lesions seemed also to occur chiefly in those cases in whom the avoidance of diabetic coma and other types of uncontrolled diabetes has been possible over long periods of time.

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High Serum Acetylcholine Concentrations in Pernicious Anemia and Their Reduction by Effective Therapy *

By
JOHN EMERSON DAVIS, Ph.D.
LITTLE ROCK, ARKANSAS

EVIDENCE BASED ON animal experiments (1, 2) tends to show that liver extract and pteroyl glutamic acid may cause remission of anemia by lowering the acetylcholine concentration of the blood serum, probably by increasing cholinesterase activity. Part of this evidence was found in the fact that continued injections of acetylcholine into dogs caused hyperchromic anemia which was responsive to antipernicious anemia treatment. Other work (3) has shown that acetylcholine derivatives can produce changes in the central nervous systems of dogs, some of which resemble changes reported to occur in human pernicious anemia.

Inasmuch as a relatively simple method for the estimation of acetylcholine in serum was developed in the above-mentioned work (2), it seemed a matter of considerable interest to determine the concentration of this substance in the sera of anemic human beings. Such determinations have been made and are the chief subject of the present report. Serum cholinesterase activity was also estimated in anemic as well as apparently normal individuals.

METHODS

Serum acetylcholine concentrations were estimated by a method which has been previously described elsewhere (2), and which employs the biological assay technique used by Chang and Gaddum (4), except that a muscle chamber of 6 cc. capacity is employed. Three cubic centimeters samples of serum were obtained from blood which had been mixed with 0.3 per cent eserine solution (3 mgm. of eserine per 10 cc. of blood) immediately after withdrawal from a vein. The serum was mixed with an equal volume of 10% trichloroacetic acid solution, shaken, allowed to stand for 10 minutes, and filtered. To the filtrate (about 2.5 cc.), was added 2.5 cc. of frog Ringer solution. This mixture, actually a solution, was then brought to a pH of about 6.6 by the addition of sodium hydroxide solutions in a total volume not exceeding 1 cc. This neutralized mixture was then substituted for the usual frog Ringer solution (adjusted to pH 6.6), in the muscle chamber enclosing an isolated, eserinated frog rectus abdominis muscle. If any response of the muscle was recorded, it was compared with the contractions elicited by standard acetylcholine solutions of known strength. The serum extract can be tested alternately

with standard acetylcholine-in-Ringer solutions, allowing 10 minutes between trials for washing and re-eserinating the muscle. Sodium trichloroacetate (2.5% in

TABLE I
Serum Acetylcholine and Cholinesterase Activity Values
in Normal and Anemic Individuals.

Subject	Acetylcholine (mcg. per 3 cc.)	Cholinesterase Activity*	R. B. C. count x (10 ⁶)	Diagnosis
Mr. J.	0.2	1.18	5.2	Normal
Mrs. U.	0.2	1.12	4.6	Normal
Mr. V.	0.2	1.57	5.0	Normal
Mr. L.	0.2	0.83	5.0	Normal
Mr. B.	0.25	1.09	5.1	Normal
Mr. W.	0.25	0.89	5.2	Normal
Mr. M.	0.3	0.13	1.3	Brill-Symmer's Disease
Mr. F.	0.25	0.36	2.7	Lymphosarcoma
Mr. G.	0.3	0.37	2.4	Hemorrhagic Anemia
Mr. N.	0.2	0.87	2.2	Sickle Cell Anemia
Mr. B.	0.25	0.25	1.7	Sprue in Remission
Mrs. S.	0.25	0.43	2.1	Myelogenous Leukemia

Pernicious Anemia in Relapse			After 4 to 7 days of treatment**			% Reticulocytes
		C			C	
A.	Ei	B.	A.	Ei		
	Ch.	R.				
Mrs. B.	0.5	0.50	1.3 x 10 ⁶	0.25	0.47	33%
Mrs. T.	0.55	0.86	2.5 x 10 ⁶	0.2	0.89	6%
Mr. D.	0.45	0.27	0.6 x 10 ⁶	0.2	0.07	18%
Mr. B.	0.5	0.27	1.0 x 10 ⁶	0.2	0.54	13%
Mr. K.	1.0	0.89	2.2 x 10 ⁶	0.25	0.78	19%
Mrs. X. P. A. in remission, back for treatment				0.3	0.69	
Mr. Y. P. A. in remission, back for treatment				0.3	0.81	

* Cholinesterase activity is expressed in terms of cc. of 0.01 N sodium hydroxide required to neutralize the acetic acid liberated in 10 minutes from an acetylcholine bromide solution by 0.5 cc. of blood serum.

** Treatment of the pernicious anemia cases was as follows: Mrs. B., 1 unit liver extract daily; Mrs. T., 40 Gm. Ventriclein daily; Mr. D., 60 mgm. of Folic Acid, intramuscularly, daily; Mr. B. and Mr. K., 20 mgm. of Folic Acid, intramuscularly, daily.

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Department of Physiology and Pharmacology, University of Arkansas School of Medicine Little Rock, Arkansas.

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Ringer solution) does not cause contraction of the rectus muscle during a two-minute exposure provided it has been neutralized to the same pH as the frog Ringer solution which it replaces (i.e., pH 6.6 or 6.8). The serum extracts were also tested on the non-eserinized rectus, to make sure that any response was not due to potassium ion, choline, or other substance whose action is not increased by eserization of the test object.

Cholinesterase activity was determined by electrometric titration with 0.01N sodium hydroxide, of the acetic acid liberated from an acetylcholine bromide solution (100 mgm. in 25 cc. water) by 0.5 cc. of serum in 10 minutes at a constant pH of 7.38 and at room temperature.

The human subjects included in this study con-

sisted of 5 pernicious anemia patients who were examined during relapse and after 4 to 7 days of treatment, and two other patients who were in therapeutic remission. Six apparently normal persons, and six anemic individuals with secondary anemias were also tested.

RESULTS

Table I shows the acetylcholine values and cholinesterase activities that were actually determined on our human subjects, together with the erythrocyte counts on most of them.

It will be seen in the table that the six "normal" individuals had 0.2 to 0.25 micrograms of acetylcholine per 3 cc. of serum, or 6.6 to 8.2 micrograms per 100 cc. of serum. Six patients with secondary anemias had

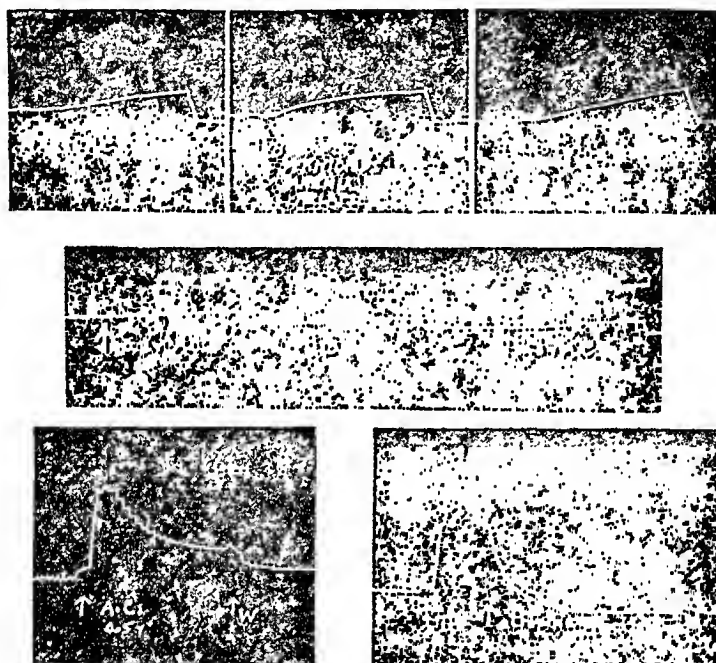


Figure 1. Experimental Record Showing the Reduction of an excessive Concentration of Acetylcholine in the Serum of a pernicious Anemia Therapy

Upper row: Contractions of the eserized frog's rectus abdominis muscle immersed in Ringer's solution at pH. 6.7 in response to 1, 0.5 gamma of acetylcholine; 2, an extract from 3 cc. of blood serum from a patient having pernicious anemia in relapse; and 3, 0.5 gamma of acetylcholine. Each contraction was allowed to proceed for two minutes, after which the drum was stopped for 10 minutes while the muscle was washed, re-eserized, and allowed to relax.

Middle row: Contractions of the eserized rectus muscle in response to 0.2 gamma A. C.; an extract of serum (B) from the same patient as above after six days of treatment with liver extract, intramuscularly; and finally 0.3 gamma of acetylcholine. The muscle showed progressive decrease in sensitivity.

Lower row: Left-Contraction of an isolated segment of rabbit duodenum immersed in Sollman-Rademacker solution at 37° C. in response to 0.5 gamma of acetylcholine, added to the bath at the first arrow. At W, the bath solution was replaced with fresh S-R salt solution. Right: at T, the muscle bath solution was replaced with an extract of serum from a patient with pernicious anemia in relapse. At the height of contraction, atropine (0.5 mgm.) was added, caused a typical relaxation.

acetylcholine concentration of the same or a slightly higher order, i.e., from 6.6 to 9.9 mg. per 100 cc. of serum. Their serum cholinesterase activities were quite variable in range, but even in those with low values, the acetylcholine concentrations were reasonably close to what may be considered normal. The serum cholinesterase values are low in those patients whose red cell counts are below 2 million, and in the single case of leukemia.

In pernicious anemia in relapse, our five patients showed markedly elevated acetylcholine concentrations in the serum (Table I), which ranged from about 15 to 33 micrograms per cent. In these patients, also, the serum cholinesterase activity was low when the red cell count was below 2 million per cubic millimeter of blood.

Three of the P. A. patients were treated with pteroyl-glutamic acid (Lederle's Synthetic L. casei factor), one was treated with liver extract, and one with stomach, U. S. P. (Ventriculin). All responded to treatment. The reticulocyte percentages shown in Table I are not all at the maximum for each patient, but were obtained near the times of the peak response. It will be seen (Table I) that the varied forms of treatment reduced the serum acetylcholine levels to normal within four to seven days. Cholinesterase activities at this time were increased in one patient, diminished in two, and virtually unchanged in two.

We can say with reasonable certainty that all values for serum acetylcholine, as listed in Table I, are probably correct to within plus or minus 0.05 meg.

Figure 1 shows an actual record of an assay of acetylcholine in a blood serum extract, on the eser-inized rectus muscle of the frog, both before and after the patient had been treated. The records at the top of the figure show a final assay, after the quantity of A. C. in the serum had been approximately estimated by comparison of its effect with contractions elicited by different strengths of known acetylcholine bromide solutions.

Practically all of the blood sera tested were assayed on two or more frog muscles. The records at the bottom of Figure 1 show contractions of a rabbit duodenal segment immersed in Sollman-Rademacker solution at 37° C., in response to, first, a definite amount of acetylcholine; and, second, a blood serum extract from a patient with P. A. in relapse. The latter contraction was quickly abolished by atropine, which caused a typical loss of tonus, and thereby more certainly identified the activity in the blood serum as acetylcholine.

DISCUSSION

The presence of a high concentration of acetylcholine in the serum of pernicious anemia patients during relapse raises the question as to whether the excess of this chemical might possibly be the ultimate chemical cause of the disease. This suggestion becomes more of a probability in view of the fact that acetylcholine

has been shown previously (2) to be capable of producing a hyperchromic anemia in dogs which is responsive to all effective anti-pernicious anemia treatments. Also in favor of this idea, is the fact that the effective treatment of pernicious anemia reduces the acetylcholine concentration of the serum to normal before any increase in the erythrocyte count has occurred. This suggests to us that a positive factor (i.e., acetylcholine) may in some manner depress or arrest the maturation of cells in the bone marrow in pernicious anemia. When the excess of this factor (hormone or metabolite) is reduced by effective treatment, one would expect that normal maturation of cells at a normal rate in the marrow would be resumed.

Such a conception of the causation of pernicious anemia does not, of course, explain how an excess of acetylcholine in the serum comes to exist. It would appear from our experiments that the serum cholinesterase activity is not far below normal in some cases of pernicious anemia. It also seems that at about the fifth day after treatment with liver or folic acid has been instituted, the acetylcholine concentration is reduced, but the cholinesterase activity (as measured) may be unchanged or even diminished. This lack of early effect of treatment upon serum cholinesterase activity in pernicious anemia is in sharp contrast with our observations upon other normal and diseased people (6) and leukemia patients (7), in whom the administration of folic acid usually caused an immediate rise in serum cholinesterase activity. It may well be that effective treatment in pernicious anemia first causes an increase in blood cell cholinesterase. Indeed, Sabine (5) has shown that the cholinesterase activity of whole blood and blood cells is low in pernicious anemia, and shows an early increase as observed on the second to fourth days following the institution of effective liver extract therapy. She also found that the serum cholinesterase activity was slightly decreased, increased, or unchanged during the first week of therapy, and this observation is confirmed in our work.

The acetylcholine concentrations found by us to prevail in the serum of normal humans are of the same order as those reported by Chang and Gaddum (4) for the blood of the horse, dog, and ox.

To the author's knowledge, the serum acetylcholine concentrations reported in this paper are the first estimations of this substance that have been made on human blood serum in health and disease.

Recently, Clarkson and Best (8) have reported their failure to produce anemia in dogs by feeding choline. These workers, however, did not do the same experiment that we performed (2, 9). They fed their animals a basic dog food enriched by the supplementary addition of dried yeast, sucrose, and tomato juice. Yeast is known to be a good source of folic acid (10), which antagonizes choline anemia. We have succeeded in producing "choline anemia" in each of the past three years and are again producing it this year. That the anemia was due to choline or acetylcholine, was

shown by the fact that atropine sulfate, given simultaneously, induced remission of the anemia (9).

SUMMARY

The acetylcholine content of 3 cc. samples of eserinizd human blood sera has been estimated biologically.

Five patients with pernicious anemia in relapse were found to have serum acetylcholine concentrations ranging from 15 to 33 micrograms per 100 cc. These values were reduced to from 6.6 to 8.2 micrograms per cent, as observed on the fourth to seventh days of effective treatment with pteroyl glutamic acid, liver extract, or Ventriculin.

Six healthy individuals with normal erythrocyte

counts had acetylcholine concentrations varying from 6.6 to 8.2 micrograms per 100 cc. of serum.

Six patients with secondary anemias were observed to have serum acetylcholine concentrations which varied from 6.6 to 9.9 micrograms per cent. Serum cholinesterase activity was low only in the most severe anemias.

The author wishes to express his grateful appreciation to: Dr. E. A. Sharp and his colleagues of the Anemia Laboratory of the Parke, Davis & Co., of Detroit, for making three of their pernicious anemia cases available for this study; to Dr. W. Seegers and the physiology department of Wayne University for space and facilities used for part of this study, and to Drs. B. B. Wells and W. Hamilton for access to patients at the University Hospital, Little Rock, Arkansas.

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Pteroylglutamic Acid Displacing Agents

By
GUSTAV J. MARTIN,
SOUREN AVAKIAN,
LEO TOLMAN,
HAROLD URIST,
and
JACK MOSS
PHILADELPHIA, PENNSYLVANIA

THE SYNTHESIS of 7-methyl folic acid and a report of its effectiveness as a displacing agent has been made (1). In an extension of this work certain other displacing agents were synthesized. These included oxypteroylglutamic acid (N-(4-(((2,4-dihydroxy-6-pteridyl)methyl)amino)benzoyl) 1 (+) glutamic acid), oxypteroic acid, pteroylaspartic acid (the aspartic acid analogue of pteroylglutamic acid), 7-methyl pteroylglutamic acid (N-(4-(((2-amino-4-hydroxy-7-methyl-6-pteridyl)methyl)amino)benzoyl) 1 (+) glutamic acid), 7-methyl pterioic acid and 7-methyl pteroylaspartic acid. The methods for the synthesis of these chemicals will be reported separately.

Each chemical was tested for its ability to displace

folic acid in the Strep. faecalis lactis R (8043) test of Mitchell and Snell (2). Folic acid concentrations were varied from 0.0065 ug. up to 1000 ug. per 10 ml. Displacing agent concentrations were varied from 1 to 10,000 ug. per 10 ml.

TABLE I
Pteroylglutamic Acid Displacing Agents

Compound	Inhibitor/Metabolite Ratio Half Maximum Inhibition
Oxypteroylglutamic acid	Inactive
Oxypteroic acid	Inactive
7-Methyl pteroylglutamic acid	2:1
7-Methyl pterioic acid	10:1
Pteroylaspartic acid	100:1
7-Methyl pteroylaspartic acid	100:1
N (4-(((4-quinazoline)amino)benzoyl) glutamic acid	Inactive as displacer Possesses "Folic acid" activity (3).

The failure of oxypteroylglutamic acid to function as a folie acid displacing agent in the system studied is particularly interesting in view of the effectiveness of oxythiamine (4) as a thiamine displacing agent. The amino group position in one case is probably of vital functional importance and in the case of folie acid of relatively slight significance. The 2 position on the pteridyl radical would seem to present a contrast to the 7 position inasmuch as 7-methyl pteroylglutamic acid is a highly effective agent. It is impossible to offer an explanation of the action of the quinoxaline compound which in itself possesses vitamin ac-

tivity. The capacity for displacement possessed by the aspartic acid analogue seems to place the glutamic-aspartic replacement system on a firm basis in view of the effectiveness of seryl glyceyl aspartic acid in displacing seryl glyceyl glutamic acid (5).

SUMMARY

7-Methyl pteroylglutamic, 7-methyl pteric, pteroyl aspartic and 7-methyl pteroylaspartic acids are effective displacing agents for pteroylglutamic acid. Oxypteroylglutamic and oxypteroic acids are inactive in the system studied.

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The Management of Pruritus Ani in the Armed Forces

By

MARK M. MARKS, M.D.
KANSAS CITY, MISSOURI

PERI-ANAL ITCHING among Army personnel, by necessity, had to be treated in such manner as to afford maximum relief with a minimum loss of time from active duty.

Every effort was first made to find the causative agents. Anal pathology such as marginal ulcers, fissures, hemorrhoids, cryptitis or papillae were surgically removed. Each patient was questioned for possible sensitivity to specific ingested material or to contact agents. In order of their frequencies, citrus fruits, their juices, wheat products, beer, tobacco and soap were found to be the most frequent inciting substances. Dietary corrections could be made only to a limited degree.

Eighty-six per cent of those suffering from chronic peri-anal itching also had moderate to severe dermatophytic involvement of the interdigital spaces of the feet. These were treated on an ambulant basis. Once each week these patients had the involved portions of their feet painted with a six per cent mixture of salicylic acid in equal parts of alcohol and compound tincture of benzoin. The peri-anal skin was moistened with water and the pruritic parts painted with an indelible pencil. The crystalline gentian violet of the pencil readily penetrates the chorionic layers of the skin. It is not painful when used in this manner and is an admirable antiseptic and fungicidal agent. Used more often, this dye can be sufficiently caustic to

produce painful burns. Self medication is limited to the use of cold water, half-strength witch-hazel or Burrough's solution. A bland ointment was prescribed to dry the parts and allay the itching; the following to be used before retiring:

<i>Menthol</i>	<i>one grain</i>
<i>Aluminum Sulfate</i>	<i>three grains</i>
<i>Starch</i>	
<i>Zinc Oxide, pulverized</i>	<i>aa two drams</i>
<i>10% Benzocaine Ointment</i>	
<i>Aquaphor</i>	<i>aa q. s. a. d. one ounce</i>

One of the important phases of this treatment was to instruct the patients in their own care. The use of toilet tissue was strictly prohibited. Soft, disposable cleansing tissue or cotton was substituted. The feet and inter-cruel areas must be thoroughly dried after bathing. If intractable itching did occur, pinching was advised instead of scratching in order to minimize trauma to the skin.

CONCLUSIONS

During a three year period in an Army medical installation* only one was so refractory to all treatment that he had to be discharged from service. Six others were tattooed with cinnabar with minimal results. Subcutaneous injection of oil soluble anesthetic gave temporary relief in four cases and sub-cutaneous neurotomy was performed in two. The treatment outlined proved to be highly effective in the majority of cases.

Submitted August 21, 1947.

From the section on Proctology, department of Surgery, Menorah Hospital, Kansas City, Missouri.

* Regional Hospital, Camp Crowder, Missouri.

Treatment of Pruritus Ani by Local Applications of Aluminum Hydroxide Gel *

By
M. H. F. FRIEDMAN, Ph.D.,
B. F. HASKELL, M.D.,
and
W. J. SNAPE, M.D.**
PHILADELPHIA, PA.

NUMEROUS FACTORS have been suggested as the causative agents for anal pruritus (1) and many forms of therapy have been attempted. However, while some of these factors may be contributory, the underlying basis of the anal itch still remains to be discovered. A review of the literature leads to the conclusion that in most instances pruritus ani is not a disease per se but rather a symptom complex of some as yet unknown pathologic process. Except in certain specific cases where the primary cause of the itch has been found to be associated with factors such as fungal infection, food or drug allergy, inflamed hemorrhoids, skin tags, and certain systemic diseases (such as diabetes and leukemia), the etiology remains unknown.

While studying the nature of the peristomal skin erosions in ileostomy and colostomy patients (2), one of us (M. H. F. F.) noted the striking similarity in appearance of this lesion with that seen in the perianal skin in certain patients with pruritus ani. In both cases the skin of the affected area may be reddened, eroded, macerated and moist. Frequently too in some patients with pruritus ani of an advanced degree, the chief complaint no longer may be that of a localized itching sensation but rather of a burning sensation similar to that said to be experienced by the patient with peristomal excoriations.

The anal skin of the patient with pruritus ani usually presents either a dry or a moist appearance and only rarely does a "dry pruritus" become a "moist pruritus" or vice versa. The skin erosions in patients with bowel fistulas are believed to be due mainly to the irritant and digestive action of the proteolytically active digestive fluids draining from the intestine (2). It occurred to us that the anal itching in patients with the moist type of pruritus ani may be due similarly to the irritant and digestive action of a proteolytically active material. The constant presence of traces of a trypsin-like enzyme in the anal region could be conceived as bringing about the characteristic irritation of the skin with the sensation of intense itching and the typical moist appearance.

Several investigators have associated the leakage of material from the anal orifice with anal pruritus. Bodkin (3) believed that "the nervous state of the patient caused some excessive or abnormal secretion to

take place in the mucosa of the large bowel . . . reduction of the secretion produces marked clinical improvement." Zweig (4) concluded that the anal itching was due to constant irritation by excrecences on the anal skin formed from material constantly discharged from the diseased rectal mucous membrane. Apparently he considered the irritation to be mechanical rather than chemical in nature. While the results of our present study were being prepared for publication, there appeared in June 1947 an interesting paper by Hoelzel (5) describing experiments he performed on himself. Following a diet of cotton fiber and fruit juice, an intense anal itch developed in association with anal leakage of small amounts of fluid. Unfortunately he did not study the nature of this fluid, but deduced that it probably had a tryptic action on the anal skin which gave rise to the anal pruritus.

To test the validity of our hypothesis, determinations of the presence of proteolytic enzymes in the anal canal were made in 56 subjects (Table I). (Of these, 32 were patients with pruritus ani uncomplicated by other anorectal pathology, 15 were patients with anorectal disease without accompanying pruritic manifestations, and 9 were patients without symptoms referable to the anorectal region and not suspected of having disturbances in bowel physiology. Material for examination was taken from the anal canal by means of a small pipette especially designed for the purpose. Material contaminated by feces was discarded. Determination of the proteolytic activity of this material was made by a modification of the Riggs-Stadie (6) photo-electric turbidometric procedure on an albumen substrate at pH 7.8. Concentrations above 8 units could be considered as unequivocal evidence of significant amounts of proteolytic enzyme.

TABLE I

	Subject	No. of cases	Cases with enzyme concentrations above 8 units
I	Pruritus Ani		
	Moist	19	15
	Dry	8	0
	Indeterminate	5	1
II	Anorectal disease (non-pruritic)	15	3
III	No gastro-intestinal pathology	9	2
	Total	56	

The results (Table I) show a positive correlation between the existence of a moist type of pruritus ani and

From the Department of Physiology, Jefferson Medical College, and the Proctologic Service of the Department of Surgery, Jefferson Hospital, Philadelphia, Pennsylvania.

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** The authors are indebted to Dr. Henry S. Bourland for data on nine patients treated by him.

the presence of measurable amounts of proteolytic enzyme in the anal canal, and strongly suggest a cause-effect relationship between the presence of proteolytic enzymes and anal itching. Other factors besides enzymatic digestion and irritation are probably also involved. Individual susceptibility of the affected area and the length of time the digestive action is permitted to proceed may be important.

Previously one of us (2) reported the successful use of aluminum hydroxide gel in the treatment of the excoriations of the skin around the fistula in patients with ileostomies and colostomies. The beneficial results were attributed to inactivation of the proteolytic enzyme and adsorption of the chemical irritants of the digestive fluid by the aluminum hydroxide. In view of finding tryptic enzymes in the anal canal of patients with the moist type of anal pruritus, treatment of pruritus ani by a similar procedure was an obvious consideration.

The aluminum hydroxide was provided for the patient's use in the form of a thick paste. This was prepared from the commercial preparations of aluminum hydroxide gel by either evaporation to the desired consistency, or else thickening by the incorporation of kaolin. The latter procedure is simpler and equally satisfactory except that the paste tends to harden and cake more readily. Addition of a hygroscopic agent may correct this. The alumina gel paste was prescribed without any additional medication. It was felt that such a procedure would permit a clearer interpretation of the effects of the paste. Patients were advised to cleanse and dry the anal area carefully after stool. They were instructed to separate the anal margins as widely as possible and to apply the paste on and between the skin folds. A fairly heavy layer was preferable, and no attempt was to be made to rub the paste into the skin. A small amount was also to be pressed into the anal canal. The paste was applied 3 to 6 times daily, the former application being gently removed with warm water before new material was applied. More frequent applications were indicated in the first few days of treatment. No vaseline or other oily material was applied since these interfere with the adherence of the paste to the skin.

During the past three years, 134 patients with pruritus ani have been treated with the aluminum hydroxide paste. The youngest patient was a boy of 16 years old, and the oldest a woman of 64. Evaluation of results of treatment based upon the statement of the patient is recognized as subject to error. However, some additional criteria were of value in determining the efficacy of the paste. In nearly every instance other forms of therapy had been employed previously. These included various lotions, ointments, fungicidal preparations, and in three instances, X-ray therapy. Therefore, some basis of comparison was available. In addition, changes in the appearance of the perianal skin offered objective evidence regarding the effects of the paste.

It soon became evident that the effectiveness of the paste depended largely upon the type of pruritus; in most of the "moist" cases response was prompt and

sustained, whereas, in the "dry" cases very few of the patients were benefited, and in some instances the distress was apparently aggravated. (Table II). The "moist" grouping refers to that type of anal pruritus in which the perianal skin is reddened, soft or macerated, and associated with a variable amount of serous fluid. The "dry" cases are characterized largely by marked hypertrophy of the skin, with thickening of the folds and deep rugae. The skin is dry, and often of a leathery consistency. Occasionally, little or no

TABLE II

Nature of Anal Skin	No. of Cases	Marked or Moderate Improvement	
		No. Cases	Per Cent
Moist	98	93	94.8
Dry	36	2	5.5
Total	134	95	70.8

gross change in the perianal skin is demonstrable.

In all instances where a favorable response was obtained, it occurred within two weeks. About the same interval of time, on the average, elapsed before definite objective changes were noted in the perianal skin. In most cases in which the paste was effective, the skin eventually assumed a normal or nearly normal appearance. Six cases representative of the patients treated with paste are summarized below. These illustrate the good response shown by the patients with the "moist" type of pruritus ani and the ineffectiveness of the aluminum paste in patients with the "dry" type:

Case 1: J. B. G., male, aged 45 years. Examined 12/5/45. Had had anal itching, diagnosed as eczema, for three years. Various topical remedies used. Anal region very moist with extensive redness, thickening, softening, excoriations and marked skin changes. Aluminum hydroxide paste applied.

12/18/45. Less itching; skin shows definite improvement.

1/8/46. No itching; skin shows few excoriations at anal verge.

2/13/46. No itching; skin grossly normal.

Case 2: M. S., male, aged 26. Examined 10/17/45. Itching began about seven years previously. Three years before this examination patient was treated for a year with various medications without relief. Itching worse under strain, and especially troublesome after stool. On examination, skin folds thickened, with hypertrophy of anterior raphe and wide zone of redness, moderately moist. Treatment with aluminum hydroxide paste begun.

10/31/45. Some improvement.

11/14/45. Skin definitely improved. Very comfortable.

12/5/45. Improvement continued. Recently under much tension, when slight itching occasionally recurred.

1/5/46. Very comfortable. Occasionally transitory itching, which causes no concern.

Case 3: McL., female, aged 40. Examined May 1945, complaining of acute dermatitis of anus extending to vulva, with ulceration of skin. Had had fistulotomy in the left anterior quadrant several years before, after which the rectal mucosa prolapsed through the anal canal, permitting seepage. Rectal prolapse repaired 9/7/45. Boric acid compresses and merthiolate cream used for pruritus without effect. Inflamed skin very moist.

9/15/45. Aluminum hydroxide paste applied. In one week itching was relieved, with skin drier and of nearly normal texture. Patient continues to improve with use of paste, and is practically free of itching.

Case 4: S. E. H., male, aged 40, Examined 9/29/45 for severe anal pruritus of many years' standing, but no anorectal pathology observed. Had had a variety of treatments and one anorectal operation elsewhere without effect. Perianal area inflamed from sacrum to inguinal region, and laterally about three inches from the anal verge on each side. Greatly hypertrophied, almost condylomatous skin, extending through the anus, with formation of large rugae, somewhat macerated. Aluminum hydroxide paste applied, with lessening of distress in twenty-four hours, and relief in forty-eight hours. Within two weeks the skin was smooth, normally elastic and flexible.

Case 5: I. S., female, aged 37. Examined 11/10/45, complaining of anorectal pain and severe itching. The skin was moist, granular and somewhat excoriated, with many tags; external and slightly prolapsing internal hemorrhoids present. Aluminum hydroxide paste applied. Itching completely relieved within one week, with dryness, reduction in size of skin tags and disappearance of excoriations.

Case 6: J. M., male. Examined August 1944, with pruritus ani. There was no anal pathology which would account for the pruritus. However, the patient had a solitary benign adenoma the size of a small pecan about 14 cm. from the anal verge. This polyp was removed by fulguration. His itching became less, but did not entirely disappear. The perianal skin was dry, somewhat thickened and had lost some of its pigment. Aluminum hydroxide paste was prescribed 9/22/45. The itching became worse, due probably to the increased dryness. The paste was used for only about one week.

Persistence in application of the paste seemed to be essential. The tendency for intermittent recurrence of itching or relapse of the anal pruritus is well known. For this reason a number of patients continued to apply the paste after cessation of itching. In some patients who discontinued treatment after being relieved of the itching sensation, there developed within a year an acute exacerbation of the condition. Itching returned usually after an episode of emotional stress or a mild gastrointestinal upset. In nearly every instance, in which the aluminum hydroxide paste was initially helpful frequent reapplication brought about early relief. In three patients, however, who had been symptom-free for a period of two to three years before another bout of itching recurred, the second course of intensive treatment with the paste was less helpful than in the initial course.

We believe it significant that the patients benefited by the application of the aluminum hydroxide paste were all among those who showed moisture continuously in the anal region. In patients with "dry" pruritus, the paste either had no effect on the itching or else aggravated the condition. Whether the beneficial effects were entirely due to inactivation of the proteolytic enzyme of the anal seepage material by adsorption we do not know. The paste had a distinct tendency to ab-

sorb fluid and dry the skin. This may have contributed in part to the comfort of at least several patients with excessive seepage of fluid from the anal canal. Finally, we may add that possibly other substances which may inhibit or adsorb trypsin will be found useful in the treatment of moist pruritus ani. However, our experience with other agents, though limited, has been disappointing, mainly because of local skin reactions. To date, no idiosyncracies to aluminum-hydroxide gel occurring among those using it or engaged in its manufacture has been reported in the literature.

The present study has shown that in patients with "moist" pruritus ani there is usually a discharge of proteolytically active anal drainage fluid. Whitney (7) acknowledges the presence of moisture on the perianal skin of approximately 50 per cent of the patients with pruritus ani but doubts that this is due to secretion from within the anus. However, the observations made by us during the course of this study and the experiments of Hoelzel (5) do not support Whitney's contention that anal leakage is non-existent. Why this discharge should occur, we do not know. Furthermore, as suggested above, in addition to the constant presence of a proteolytic enzyme in the anal region, it is also probable that other factors, such as specific local skin sensitivity, may be involved. In patients with extensive diarrheas, there is sometimes present a scalding sensation referable to the anus, but the typical itch experienced by the patient with pruritus ani occurs infrequently. Recently we had occasion to study a series of 57 patients with non-specific ulcerative colitis (8). Some of these patients had as many as 20 and 30 loose bowel movements daily. While pain in the rectum and a scalding sensation in the anus were frequent complaints, in only one patient was a sensation of intense itching described.

SUMMARY

The moist perianal skin found in many patients with pruritus ani is probably due to leakage of material from the anal orifice. This drainage material has been found to have enzymatic properties similar to trypsin. The constant presence of traces of such proteolytically active material in the anal region may be responsible for the skin irritation with the attendant sensations of intense itching. Local applications of a paste made from aluminum hydroxide gel brought prompt sustained relief to 93 out of 98 patients (or 94.8 per cent) with the "moist" type of pruritus ani but was effective in only 2 out of 36 patients (or 5.5 per cent) with the "dry" type of pruritus ani. The beneficial effects of the aluminum hydroxide are probably due to the adsorption and inactivation of the proteolytic enzyme or other chemical irritants in the anal drainage fluid.

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Bacteriology of Diarrhoeal Diseases

By
ALFRED J. CANTOR
FLUSHING, N. Y.

LET US CONSIDER the role of bacteria in diarrhoeal diseases. More than sixty different bacterial organisms have been found in stool specimens. These are normally present. They do not produce disease in an otherwise normal intestinal tract. We should, therefore, consider the factors that might reduce resistance sufficiently to permit these organisms to produce disease.

Infection may be overwhelming. The organisms may be unusually virulent. Then again, the individual may, for many reasons, develop a lowered resistance. Any one of these factors would be enough to permit the development of colon disease.

The intestinal contents of the new-born are sterile. As the usual milk feeding begins gram positive bacilli of the acidophilous type appear. Later the gram negative colon bacilli are found, and these increase in number as we approach adult life.

Although many organisms may be swallowed with the food, such as tubercle bacilli, yeasts and sarcinae, spirchetes and cocci, the normal gastric contents become sterile within three or four hours after eating. This is due to the acid concentration. Similarly very few pathogenic bacteria will grow in the duodenum, and the small intestine is usually free from pathogens.

Of course there are useful bacteria in the intestinal tract. Bacteria of the acidophilic group are present in the small intestine. These organisms split carbohydrate and produce organic acids such as lactic and acetic acid. The colon bacilli of the large bowel split protein, under anaerobic conditions splitting off the amino group. This effect is particularly evident when there is inadequate carbohydrate in the diet. Under aerobic conditions the carboxyl group is split off. It is very likely that there are also bacteria in the bowel that split fats into fatty acids and glycerol, and others that act in the hydrolysis of cellulose.

Normally present in the feces are four large groups of bacteria. These are: (1) The colon group. (2) Streptococci. (3) The anaerobes, and (4) The lacto-bacillus group. There are other less common organisms such as the bacillus proteus, the bacillus pyocyaneus, the bacil-

lusfaccalis alcaligenes, and the bacillus lactis aerogenes.

Of course, as we have indicated above, the bacterial flora of the colon is closely related to the type of food ingested. The lacto-bacillus group predominates during the period of milk feeding. The colon bacillus predominates during the period of mixed diet. The colon bacillus, of course, acts upon protein as we have above indicated. If the adult lives on a protein diet the colon group and anaerobes are in the great majority. If the diet is purely carbohydrate the lacto-bacillus groups would be most numerous.

Another factor influencing the number of bacteria and their type would be the degree of hydrochloric acid secreted by the stomach. In conditions of achlorhydria, such as in pernicious anemia, there would be an increase of the bacillus coli, streptococci, and the bacillus welchii. On the usual normal mixed diet containing proteins such as meats, fish eggs and poultry, the normal ratio of gram positive to gram negative organisms in the colon is approximately 1:10. If these food elements are eliminated from the diet, within a period of several weeks the gram positive bacillus acidophilous type of organisms replace the colon group. The rapidity of this change may be increased by administering one or two ounces of lactose daily.

The streptococcus is considered to be more often a source of pathogenic activity than any of the other bacteria present in the colon. The non-hemolytic streptococci, (enterococci) are the dominant strain. It would seem that the streptococci, just as other organisms normally found in the colon, are secondary invaders in most colon disease.

Spirochetes are occasionally found on microscopic examination of fecal smears. Their clinical significance is not known. They may be swallowed, (the spirilla of Vincent), or may come from bronchial secretions. They are usually considered saprophytic.

Fungi are very frequent in the feces. It is not likely that any of the fungi to be found in the stool in patients in the United States are the cause of diarrhoea. A possible exception may be certain sprue-like conditions.

The blastocystis hominis is frequently found in the feces. It is not considered pathogenic. As we have

stated, certain organisms are swallowed with food. These organisms are spore-bearing bacteria, spirochetes, yeasts, and sarcinae, gram-positive cocci, leptothrix-like organisms, sometimes tubercle bacilli, and gram-positive cocci, sometimes the bacillus subtilis and lactic acid bacilli. Streptococci, staphylococci, and lactis aerogenes may be found in the duodenum and jejunum. In the ileum we find large numbers of the gram-negative group of coliform bacilli. Anaerobes and spore-bearing aerobes are found in large numbers also.

We are now ready to consider the role of the pathogenic organisms. As we have stated, the above organisms are normally found in the intestinal tract. They are not usually pathogenic. Assuming normal resistance, and assuming otherwise normal conditions, these organisms do not produce disease. The bacteria we are about to consider do commonly produce intestinal disease and diarrhoea.

The typhoid bacillus and the salmonella bacillus find optimum conditions for growth in the small intestines. Other organisms that thrive in the small intestine are the tubercle bacilli and sometimes the cholera bacilli.

In the right colon, (the caecum and the ascending colon) the tubercle bacilli, protozoan parasites, the Shigella, streptococci and staphylococci find a favorable medium for growth because the stool normally becomes dry during its passage through the right colon, and the less liquid medium of the left colon is not favorable for bacterial growth. Of course, under abnormal circumstances, and especially in case of hypermotility, the stool remains liquid in the left colon. Under such circumstances the bacteria do grow and increase in number tremendously in the left colon.

We may classify the organisms responsible for diarrhoeal disease under the headings of *protozoa*, *bacteria*, and *intestinal parasites*.

Under the *protozoa* we may list the following:

- 1.) Entamoeba histolytica; 2.) Giardia lamblia; 3.) Balantidium coli; 4.) Chilomastix mesnili; 5.) Isospora hominis; 6.) Trichomonas hominis; 7.) Isospora bigeminum; 8.) Leishmania donovani; 9.) Plasmodium falciparum; 10.) Dientamoeba fragilis; 11.) Toxoplasma gondii.

Under *bacteria* we may list the following: 1.) Shigella strains; 2.) Streptococci; 3.) Salmonella group; 4.) Tubercle bacilli; 5.) Cholera vibrio; 6.) Treponema pallidum; 7.) Bacillus typhosus; 8.) Occasional invaders: a.) Staphylococcus; b.) Pneumococcus; c.) Friedlander's bacillus; d.) Bacillus proteus vulgaris; e.) Bacillus pyocyaneus; f.) Bacillus necrophorum; g.) The influenza bacillus.

Under separate heading we might list the virus of lymphogranuloma venereum. Under the *intestinal parasites* we may list: 1.) Hookworm; 2.) Oxyuris vermicularis; 3.) Ascaris lumbricoides; 4.) Trichinella spiralis; 5.) Trichuris trichiura; 6.) Strongyloides intestinalis; 7.) Tape worms: a.) Taenia saginata solium; b.) Diphylobothrium latum; c.) Hymenolepis nana; 8.) Fasciolopsis buski; 9.) Schistosoma mansoni and japonicum; 10.) Heterophyids; 11.) Oesophagostome.

In a discussion of diarrhoea caused by bacteria it is thus seen to be necessary to consider a very large group of organisms. It must be recognized that there are over forty different types of dysentery bacilli classified under the genus Shigella. In addition to the dysentery of Shigella, there are dysenteries produced by the salmonella, tubercle bacilli, the streptococci and staphylococci, the treponema pallidum, the gonococci and the typhoid bacillus, the cholera vibrio, the tubercle bacillus, and other less frequent invaders, as we have indicated above.

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Editorial

THE DANGERS OF GOING TO BED

ONCE UPON A TIME, rest in bed was considered an important therapeutic measure, but the current vogue is to keep people on their feet.

Many persons rather liked to get sick just to get in bed, but the one place on earth where peace formerly could be obtained is coming to be regarded as the real danger-spot in our civilization.

Medical authors are coming forward daily with fresh arguments against beds. R. A. J. Asher,* M.D., M.R.C.P., the most recent protagonist of bedlessness, begins by quoting from Hymns Ancient and Modern (No. 23, Verse 3):

"Teach me to live that I may dread

"The grave as little as my bed"

Then he continues in a mood of revolt — "It is my intention to justify placing beds and graves in the same category and to increase the amount of dread with which beds are usually regarded."

The learned gentleman proceeds with great skill, to show the complete debacle of the human being in bed. No organ-system is immune to the devilish deterioration which transforms the bed-ridden individual.

Hypostatic pneumonia, thrombosis and embolism, bed sores, foot drop, muscular wasting, osseous calcification with its sequela of renal calculi, incontinence, gas, constipation, fecal impaction, piles, the bed-pan complex, lethargy, insomnia, despair, nocturnal restlessness, fussiness, irritability — these are a few of the hazards, yet he admits, "I have not mentioned the loss of education in children who are long in bed, or spoken of the dangerous dust that arises during bed making." Being put to bed may result from a mere whim as when, "too often the sister puts all

her patients back to bed as a housewife puts all her plates back in the plate-rack — to make a generally tidy appearance."

Eheu! Long before Asher, the proctologists began the new revolution by denying their victims horizontal satisfaction. Before that Sir James Mackenzie, following his own cardiac infarction, almost completely scorned the bed. Thomas Edison tolerated an army cot next to his desk at Fort Myers as a mere concession to custom. Then came early ambulation which has swept the country. Physicians took their cue from the surgeons and began to think twice before falling in the old error. Today one must be critically ill (or own a policy in an insurance company) to get a hospital bed at all. Staying up has become popular. Asher merely crystallized the general feeling with caustic diatribe to emerge as the new prophet of the marathon conception. If Asher does not weaken, a profound effect will be exerted on medical therapeutics, hospital architecture, and even the home-furnishing business. We cannot be blind to the effects of the obvious corollary — if sick people stay up, why should healthy persons go to bed?

To a man of feeling all this presents a distressing dilemma. Of course, the *chair* might provide a reasonable compromise, but here again one can foresee such unfortunate results as lumbo-sacral strain, prostatism, varicose veins, fracture from falls, wristdrop (if the chair has arms) or even Saturday night palsy (if the individual sits down backwards).

Why not face facts? What we need is not early ambulation but *perpetual* ambulation. This movement, instigated by doctors, will progress rapidly until the public (who always take our advice) have turned irrevocably against both beds and chairs. Even now it is too late to begin a "back to bed" campaign. We have played into the hands of the Christian Scientists — obviously fatigue is mere error! Let's keep walking.

* The Dangers of Going to Bed. British Medical Journal, Dec. 13, 1947, 967-968.

Book Reviews

Compendium of the Parasitic Worms in Men.—Kompendium der parasitischen Wuermer im Menschen.

By Dr. Hans A. Kreis. Pp. 136. 70 illustrations. (Swiss Franks 10.00). Benno Schwabe & Co. Basel. 1947. U. S. A.: Grune & Stratton, New York.

This book, written in German and published in Switzerland, deals with intestinal parasites. The first part is devoted to its history. It further discusses the

development and biology of parasites in men. It describes the symptoms in such conditions. The eosinophilia, the toxic influence of these parasites, and the influence of the diminution of the nourishment on the host are ably dealt with, and also the mechanical damage due to the presence of the worms.

The second part deals with the types in helminthiasis. The different types of examinations are dis-

cussed and the serological examinations are well described.

The third part deals with the three different types of parasites (trematoda, cestoda, and nematoda). In this section, illustrations of the different parts of the parasites and their appearance in the examination, make this book especially valuable. The therapy is thoroughly discussed.

This book can be recommended to all those who are interested in this field. The type is attractive, the illustrations are excellent.

Franz J. Lust

Le Sel en Biologie --- A Study Concerning Sodium Chloride in Physiology and Pathology.

By P. Lonyot. Pp. 254, Masson et Cie, Paris, (1947).

The biological problems concerning salt are limitless. The presence of salt is essential to all the biological exchanges within the cells and salt is related to many elements, mineral and organic, especially water. We still do not completely comprehend its entire significance. The present volume is a synthesis and review of articles dealing with saline metabolism, both in the normal and in the diseased body, as well as in experimental animals. The final section of the book contains therapeutic deductions applicable clinically and in the laboratory. The author has produced a useful and exhaustive contribution to a very basic subject.

Diabetes Mellitus in General Practice.

By Arthur R. Colwell, M.D., Pp. 350, (\$5.25), The Year Book Publishers, Inc., Chicago, 1947.

The author has produced a "safe" book because he has avoided hearsay and legend and, by taking his own extensive career in diabetic practice and experiment as a basis, he consistently gives convincing reasons for his beliefs and attitudes. (Incidentally, he is one of the few medical authors whose introduction contains a chivalrous "thank you" to his wife for her widowhood during the writing of the book). He regards the work of Banting, Best and Collip as an unprecedented instance of perfect professional cooperation in research and recommends it to others. His

omission of the name of McLeod from the book strikes the reviewer as just. He describes as "labile" those severe cases of diabetes in which one cannot predict the day-to-day reaction of the patient to insulin-diet therapy. Three quarters of the volume is devoted to treatment. The author has not erred, as some writers have erred, in omitting reference to the neuropathological aspects of diabetes. His remarks on the action of mixtures of regular and protamine zinc insulin are very valuable. Pregnancy as well as renal disease in diabetes is well covered. Few books on diabetes, irrespective of their length, have provided as good a guide as this one to the problems in every physician's practice.

The Pathology of Nutritional Disease.

By Richard H. Follis, Jr., M.D., Pp. 291, (\$6.75). Charles C. Thomas, Springfield, Illinois, 1947.

This book gets "down to cases," by which is meant that the author is careful to avoid the blurred edges of this vast subject and to write about nothing except what is thoroughly proved. Taking the 40 substances which are generally admitted to be nutritionally essential, he shows what kind of tissue changes (and altered physiology) occur when each is deficient in the diet. No cases of multiple deficiency are dealt with. Having completed this record, the author then attacks the problem from the angle of pathological anatomy, dealing with each kind of tissue in the body and describing how each is specifically affected by single-substance deficiencies. A comparatively small fraction of the work deals with the human merely because apart from the well known deficiencies which are met with in man, there are few single-substance deficiencies which have been proved and, fortunately for man, there are many deficiencies which the author thinks could scarcely occur in man under ordinary conditions, or even under the most carefully "rigged" experimental diet. This book should be used by all physicians seeking sound knowledge in a field all too confusing and discouraging, and will unquestionably provide a work of ready reference for nutritionists themselves. Physically, the volume is exceptionally attractive, and contains not only a profusion of large half-tones of gross and microscopic specimens but a very large bibliography, and causes one to feel that format here achieves something near perfection in its own right.

Abstracts Of Current Literature

ABSTRACT EDITOR — M. H. F. FRIEDMAN

Jefferson Medical College

1025 Walnut Street

Philadelphia, Pennsylvania

CLINICAL MEDICINE

MOUTH AND ESOPHAGUS

KING, J. D.: *Experimental investigations of paradontal disease. VI. Further clinical studies of sugar-cane gnawing in treatment of gingival disease.* (Brit. Med. Jour., Dec. 20, 1947, 987-991).

In ferrets suffering from tartar deposits, the gnawing of bones eliminated paradontal disease. Since Jamaican natives were reported to be relatively free from gingivitis, it was considered that their habitual consumption of sugar cane might be responsible. Supplies of sugar cane were obtained and the effects of cane-gnawing were observed in the treatment of gingivitis in adults and institutional boys. The most striking results of the eight week tests were the extremely rapid cessation of bleeding and soreness of the more severely diseased gums and the marked improvement in dental and interdental hygiene in all cases after daily gnawing of the short lengths of longitudinally split sugar cane. Probably the value of cane-gnawing is limited to its cleansing effects and to stimulation by friction of resistance to injury of those aspects of the gingivae accessible to such friction.

WHEELER, D.: *Diverticula of the foregut.* (Radiology, October 1947, Vol. 49, No. 4, 476-481).

Under this embryologically correct but aesthetically unpleasant title, Wheeler describes esophageal-pharyngeal diverticula as well as those of the stomach and duodenum. He emphasizes the fact that only the esophageal-pharyngeal diverticula produce definite symptoms. Those in the lower esophagus may interfere with instrumentation. Generally speaking, the significance of the foregut has been greatly exaggerated.

LAHIRI, K. D.: *Melanoglossia due to penicillin therapy.* (J. Indian Med. Assn., Feb. 1947, Vol. 16, No. 5, 159-160).

The author describes black tongue occurring in a patient receiving oral penicillin and rapidly disappearing after discontinuance of the penicillin. He was be-

ing treated for gonorrhea and was also taking sulphonamides.

STOMACH

OGILVIE, SIR HENEAGE: *The early diagnosis of cancer of the esophagus and stomach.* (Brit. Med. Jour., Sept. 13, 1947, 405-407).

This is a plea for reliance on clinical findings and judgement in spite of negative roentgen findings. As the author brilliantly concludes, "I would conclude by repeating that the early diagnosis of cancer in any internal organ depends, in the main, on clinical judgement, on the early confirmation of what can, in most cases, be no more than a suspicion. We can all remember instances of a diagnosis of malignancy made on clinical grounds, of repeated examinations by experts giving repeated denials, of confirmation coming too late for curative treatment. When cancer is in question we should accept the negative warning of a penny weighing-machine in preference to the positive reassurance of the ten-guinea Harley Street expert. And if our suspicions continue, if the weight continues to fall, we must insist on an exploration. There is more rejoicing in heaven over the one laparotomy that fails to find cancer than over the ninety-and-nine (positive ones) that find it too late."

NIMEN, W.: *Emptying of the normal stomach in altitudes.* (Rev. Gastroenterol., Nov. 1947, Vol. 14, No. 11, 763-775).

Retardation of the emptying of the stomachs of persons in Mexico City, both inhabitants and visitors, appears to be due first to the anoxia caused by the increased altitude and second, the heavy use of fats in the Mexican cuisine.

MATZNER, M. J.: *Linitis plastica with total gastrectomy.* (Rev. Gastroenterol., Nov. 1947, Vol. 14, No. 11, 800-805).

A case of successful total gastrectomy for linitis

plastica. due to scirrhus carcinoma is described. Occasionally the condition is due to chronic inflammation or syphilis rather than cancer. Total removal of the stomach is justified by our increased technical and selective experience and adds comfort and often years to life.

ROBNETT, A. H. AND JONES, T. E.: *Volvulus of the stomach (report of 3 cases)*. (Cleveland Clinic Quarterly, Oct. 1947, 239-245).

All 3 cases were operated upon. Two cases were of the "complex organo-axial type" complicating diaphragmatic hernia, while the third case was of the "idiopathic organo-axial type" with gastropnoxis and congenital deficiency of the gastro-hepatic omentum and gastro-colic omentum. Symptoms included upper abdominal pain and distention with vomiting. The diagnosis is made by X-ray examination.

RAFSKY, H. A., NEWMAN, B., AND JOLLIFFE, N.: *The relationship of gastric acidity to thiamine excretion in the aged*. (J. Lab. Clin. Med., Vol. 32, p. 118, Feb. 1947).

Thirty-one healthy elderly inmates of an institution were subjects of this study. Acidities of the gastric contents after a water and toast test meal were determined as well as the thiamine content of 24-hour urine collections. The dietary thiamine intake was adequate.

The thiamine values were not related to the acid secretory ability of the stomach. Cases of anacidity and hyperchlorhydria were found among the elderly subjects but these were not distributed in relation to the level of thiamine excreted by them.

F. X. Chockley

ANNEGERS, J. H. AND IVY, A. C.: *The effect of dietary fat upon gastric evacuation in normal subjects*. (Am. J. Physiol., Vol. 150, p. 461, Sept. 1947).

Thirty normal subjects were given test meals of constant weight, volume, and caloric value but containing varying amounts of total fats. Four hours after the test meal the stomach was outlined by means of a small amount of barium and an X-ray taken. Changes in volume of the stomach were calculated from the area of the stomach. Delay in gastric evacuation was noted when the fat content of the test meal was in-

creased. Lard and hydrogenated vegetable oil (Crisco) had the same delaying effects. The inhibition of gastric emptying produced by the addition of fat was a consistent characteristic for given individuals.

W. D. Beamer

BOWEL

FORNEY, J. M., ESTRIDGE, M., AND SHAWER, J. S.: *Regional enteritis* (South. Med. J., V. 40, No. 9, Sept. 1947).

The authors present a case of regional ileitis 9 years subsequent to surgery for a perforated appendix in 1936. Symptoms of loss of weight, vague abdominal pain, and vomiting, occurred in 1945. The authors presume this condition was due to a previous inflammation in this area and that the predisposing cause was circulatory. The authors base their views on observations made at the time of operation. It was noted that the interference with mesenteric circulation was a result of the presence of bands involving the blood vessels in a localized area.

They conceive this condition may include two types: (1) circulatory, which is usually brought on by previous intra-abdominal inflammation but may occur without previous inflammation; (2) a vasomotor disturbance of the nervous mechanism. They suggest a possible cure may be in the treatment of the sympathetic nervous system following resection.

J. Meadoff

COOK, G. T. AND MARMION, B. P.: *Gastro-enteritis of unknown etiology (an outbreak in a maternity unit)*. (Brit. Med. J., Sept. 20, 1947, 446-450).

An outbreak of gastro-enteritis among mothers, staff, and babies in a maternity unit is described. The disease was characterized in adults by diarrhoea, slight fever, a watery stool of light yellow color, and, in some patients, by neutropenia. The babies had milder symptoms consisting of loose green stools sometimes accompanied by excoriated buttocks. Salmonellae, Shigellae, paracolon bacilli, and protozoa were not found to be responsible for the disease. The incubation period in adults was one to three days. The period of infectivity appeared in a few adult patients to be as long as 26 days from the onset of diarrhea. A "follow-up" of the discharged maternity patients revealed that 26% developed gastro-enteritis after discharge and that 15

to 24% of the families of returning sick maternity patients became infected. Epidemiological investigations indicate that new admissions could have been infected from overt, atypical, or convalescent cases of gastroenteritis or from carriers of the disease in the staff. It is also suggested that infection of infants in a common nursery might account for the occurrence of sporadic cases among mothers in different wards in the unit. The outbreak appears to be an example of a common and widespread disease in the special circumstances of a maternity unit which had apparently facilitated its spread.

SOKOLOFF, B.: *Biological premises for the treatment of colitis*. (Rev. Gastroenterology, Oct. 1947, V. 14, No. 10, 704-717).

One thousand cases suffering from colonic disturbances were treated with *trilactic* (an anhydrous form of lactic acid). The author favors the view that the bacterial flora of the colon is an underlying factor in disturbances of the colon. The method of treatment used "changes" the flora. Roughly one-half of the "functional" cases (irritable colon, mucous colitis) recovered. About one-fifth of the cases of ulcerative colitis recovered and so did one-half of the cases of anebic ulcerative colitis.

SHAPIRO, S. AND ASTRACHAN, J. E.: *Proctological manifestations in systemic disease*. (Rev. Gastroenterol., Nov. 1947, V. 14, No. 11, 786-800).

The author presents some 26 systemic diseases which produce proctological manifestations.

DOUB, H. P.: *Malignant tumors of the small intestine*. (Radiology, Oct. 1947, V. 49, No. 4).

Recognition of malignant tumors of the small intestine depends upon evaluation of symptoms but mostly on careful X-ray study, especially the serial films of the small bowel. Adenocarcinomas are the most common tumors. There is progressive weight loss and some degree of anemia, while pain is a prominent symptom.

HARRIS, A. M.: *A pathological survey of the appendix*. (J. Lancet, Oct. 1947, V. 67, No. 10, 355-357).

On histological examination, appendices which have been removed show a number of classifiable conditions.

The most common diagnosis was "scarred appendix" which shows increase of fibrous tissue, although the various layers are normal. Acute appendicitis is next most common showing necrosis of the mucosa. Other classifications include foreign bodies, peri-appendicitis, mucocele, fibroma, carcinoid, oxyuriasis, fecalith, stenosis and lymphoid hyperplasia. Those diagnosed microscopically as chronic appendicitis were few in number (slightly over 1 per cent): they showed a definite fibroblastic activity and mononuclear inflammatory cell infiltration, which could be interpreted as representing a chronic inflammatory process. "Constipation" may be diagnosed, in persons using cascara, by finding a brown pigmentary discoloration of the phagocytes of the submucosal area.

JONES, H. I. AND FENNER, F.: *Infection with Salmonella Blegdam amongst natives of New Guinea*. (Med. J. Australia, Sept. 20, 1947, V. II, No. 12, 356-362).

The clinical and pathological features of 14 cases of *Salmonella blegdam* infection in New Guinea natives are tabulated, and the clinical histories and post-mortem findings in four fatal cases at Lae are fully described. As in Australian soldiers, infection usually causes salmonella fever or septicemia, although one patient with salmonella gastro-enteritis and one healthy carrier were seen. Severe acute hemolytic anemia was a feature of several cases in natives from the mountain villages behind Lae. The post-mortem findings in the cases in which death occurred in the second week were those of acute septicemia, accompanied by jaundice in some cases and cystitis in others. When the infection had been more prolonged, widespread abscesses and involvement of the urinary tract were features of the post-mortem examination. Peyer's patches always appeared normal, but hemorrhages and small erosions occurred in the mucosa of the colon in one case in which *Salmonella blegdam* infection followed an attack of Shiga dysentery and in one other case. Two cases of *Salmonella blegdam* infection in Australian service personnel infected in Morotai and in Australia respectively are briefly described.

PANCREAS

DE VIDAS, J.: *Acute hemorrhagic necrosis of the pancreas, with acute intestinal obstruction, followed by recovery*. (Med. J. Australia, Sept. 13, 1947, V. II, No. 33, 333-334).

A case is described in which a correct diagnosis of

acute pancreatitis was made clinically and although the patient developed fluid in the left pleural cavity and paralytic ileus he would apparently have made a recovery without operation, by reason of medical management (fluids, suction, etc.) had he not developed a definite acute intestinal obstruction. At operation, recent tough fibrinous adhesions binding down the ileum were cut. Areas of fat necrosis were observed, as well as blood fluid in the peritoneum. He made a good recovery. The author states that the cause of acute pancreatitis is unknown.

GAMBILL, E. E.: *Chronic relapsing pancreatitis: a review of cases in which disease of the biliary or gastro-intestinal tract did not co-exist.* (Proc. Staff Meet., Mayo Clinic, Nov. 26, 1947, 537-542).

Chronic pancreatitis usually is a relapsing painful progressive disorder which affects all age groups but is more common in males than females. Early in the disease disturbance of the pancreatic function may be demonstrated only during the acute exacerbations. Eventually, owing to progressive destruction of the pancreas, its function becomes permanently deficient. Until destruction of the pancreas becomes extensive enough to produce diabetes mellitus, steatorrhea, calcification and pseudocysts large enough to be palpable, the history of recurring seizures of pain may be the sole evidence of the disease when the patient is studied in the intervals between exacerbations.

KRISTAL, J.: *Cystic and other changes in the pancreas of rats fed on a diet of mealie meal and sour milk.* (S. African J. Med. Sci., June 1947, V. 12, No. 2, 47-52).

Gross pathological reactions were noted in the pancreas of 18 of 30 rats fed a diet consisting of maize meal porridge and fermented milk. These consisted of qualitative and quantitative change in the secretory granules, associated with a patch of degranulation of the acinar cells. Later, the intercalated ducts appear to be increased in number, to be followed by a cystic dilation and disappearance of the acinar cells. The final picture was represented by a mass of dilated tubules embedded in adipose tissue. Such reactions affected the gland in a patchy fashion. Many of the rats with grossly pathological livers did not exhibit any noticeable changes in the pancreas, whereas all the diseased

pancreases were associated with severe disease of the liver.

BAGENSTOSS, A. H.: *Chronic relapsing pancreatitis; a review of the pathological anatomy in cases in which disease of the biliary or gastro-intestinal tract did not co-exist*; AND COMFORT, M. W.: *ditto, its clinical course, sequelae, diagnosis and medical treatment.* (Proc. Staff Meet., Mayo Clinic, Nov. 26, 1947, 542-552).

Grossly the pancreas in cases of chronic relapsing pancreatitis is indurated and sometimes nodular. Atrophy occasionally is present and fat infiltration sometimes extensive. Masses of fibrous connective tissue separate the parenchyma into irregular islands. Pseudocysts varying in diameter from 1.0 to 20.0 cms., were encountered in four cases. Macroscopic calcification was found in three cases. Residual necrosis was a rather common finding and probably resulted from an inflammatory process closely related to so-called acute hemorrhagic pancreatitis, but of sub-lethal type. The pseudocysts probably resulted from acute inflammation, necrosis and subsequent digestive action of liberated pancreatic enzymes. The perineural distribution of lymphocytes seen in four cases may explain the intense pain suffered by these patients. Chronic relapsing pancreatitis may represent the summation of repeated attacks of acute interstitial pancreatitis or repeated sub-lethal attacks of acute hemorrhagic pancreatitis, or in some cases a combination of the two.

Acute painful exacerbations of long duration are characteristic of the disease, but damage to the pancreas can be demonstrated only during an attack, by finding transitory elevation of the values for enzymes in the serum and equally transitory glycosuria and hyperglycemia. Sometimes the pseudocysts can be felt and in some cases an abdominal film will reveal extensive gross calcification. Fatty stools may be found. Diabetes developed in seven of the 29 cases studied critically. The pancreas may be enlarged and cause duodenal obstruction with vomiting. It may partially obstruct the common bile duct, producing transitory or chronic jaundice. Duodenitis, gastritis, gastro-intestinal hemorrhage and delayed emptying of the stomach are further complications. Death is sometimes due to acute hemorrhagic necrosis but is more often due to cancer, cerebral accidents and intercurrent infection. When disease of neighboring organs has been excluded, chronic relapsing pancreatitis is suspected because of a history of repeated attacks of epigastric pain, especially se-

vere pain lasting more than two days or located in the left epigastric region, and by a mass in the region of the pancreas. Most patients gave a history of using alcohol, and the forbidding of alcohol is important in treatment. Diabetes should be treated in its own right and steatorrhea responds fairly well to 15 grams of pancreatin daily. Surgery alone offers prolonged relief from the painful attacks.

LIVER AND GALLBLADDER

BARKER, W. H.: *The modern treatment of cirrhosis of the liver*, (South. Med. & Surg., Oct. 1947, V. 109, No. 10, 325-335).

Probably nutritional deficiency is a definite factor in cirrhosis of the liver and alcoholism plays a subsidiary role. The central consideration in the modern therapy of cirrhosis is the Patek dietary regimen — the diet is largely meat, milk, eggs, fruit and green vegetables. It contains 3600 calories (protein 139 gms., fat 175 gms., and carbohydrates 365 gms.). Vitamins, particularly the vit. B complex group are added.

PERSSE, J. D. AND HEAVNER, L. E.: *Echinococcus cysts of the liver*. (Alexander Blain Hosp. Bull., Nov. 1947, V. 6, No. 4, 143-151).

Two cases of Echinococcus Cysts of the liver occurring in Michigan are described and, because of the likelihood that service men will bring the disease to America, the authors describe the disease in considerable detail. The normal habitat of the *tania echinococcus* is the intestinal tract of the dog, man becoming infected via dog feces. The commonest site for the cyst formation is the right lobe of the liver. Apart from such symptoms as might be expected from a space-occupying mass in this region, one should look for eosinophilia which may reach 30 to 40 per cent. In the case of perforation of the cyst into the peritoneal cavity, itching of the skin, urticaria, collapse and even coma may result. Marsupialization in a one or two stage operation is the method of choice in treatment.

HEWLETT, J. S. AND ERNSTENE, A. C.: *Brucella abortus infection of the gallbladder treated with streptomycin*. (Cleveland Clinic Quarterly, Oct. 1947, V. 14, No. 4, 258-263).

This is a report of a case of active brucellosis in which *Brucella Abortus* was cultured from bile obtained by duodenal drainage. Treatment with streptomycin resulted not only in control of the patient's symptoms but also in persistently negative subsequent cultures of the bile.

ULCER

CRILE, G.: *Transabdominal vagotomy versus gastric resection in the treatment of duodenal ulcer: a comparison of results*. (Cleveland Clinic Quarterly, Oct. 1947, V. 14, No. 4, 264-270).

The author believes the transabdominal vagotomy accompanied by pyloroplasty or gastroenterostomy is safer than gastric resection. Pyloroplasty or gastroenterostomy should be done following vagotomy to facilitate emptying of the denervated stomach. Resection should be left as an "ace in the hole" till later, in case the ulcer should recur.

ALEXANDER, F.: *Treatment of a case of peptic ulcer and personality disorder*. (Psychosom. Med., Sept.-Oct. 1947, V. 9, No. 5, 320-330).

This is a very detailed account of the psychotherapy employed on a young man suffering from chronic peptic duodenal ulcer, which apparently resulted in as good a cure (if not a better one) than might have been obtained from ordinary medical treatment. The patient's emotional reactions were altered by the treatment and this obviously caused the physical improvement. The symptomatic improvement took place parallel to the development of an openly dependent transference relationship and with profound changes in the dynamic structure of his personality. The chief changes included achievement of tolerance toward accepting a certain amount of dependence upon others without shame. The technique employed by Alexander in this case consisted of 36 interviews over a period of about 10 months, with some long periods during which no treatments were used. The recitation of dreams was a prominent feature of the "talks" and their interpretation by the author displays signal skill. In the jargon of the analysts, most of the dreams contained "pregenital and phallic material and early castration fears." Emotional maturation was started as a result of these interviews, and the prognosis appeared favorable. It is noteworthy that Alexander favors this comparatively simple type of treatment to psychoanalysis which latter invites the risk of a "permanent transference neurosis."

BERNSTEIN, B. M.: *Histamine in the treatment of peptic ulcer.* (Ann. Intern. Med., V. 26, p. 852, 1947).

Medical and surgical procedures for the treatment of peptic ulcer have been aimed mainly toward reduction of gastric acidity. Though acid and pepsin may have a bearing on the causation of ulcer, the disappearance of ulcer symptoms and of the ulcer defect may occur without reduction of gastric acidity. Bernstein treated 75 patients with peptic ulcer by daily injections of 0.2 mg. histamine phosphate. The histamine stimulates gastric secretion, it is also a vasodilator drug. The theory was that the benefits from the vasodilation would be much greater than the harm from the increased acid secretion.

Men predominated in this study by 5 to 1; the ages ranged from 21 to 65 years; all patients were showing active ulcer symptoms when histamine injections were begun. The diet was liberal but of the bland type; tobacco was prohibited.

Two-thirds of the patients showed complete relief from pain after the fourth injection; 82 per cent of the patients were relieved by less than ten injections; The treatment apparently prevented recurrences of symptoms if instituted as a prophylactic measure before the seasonal advent of symptoms. No patient showed untoward reactions. The symptomatic relief noted was maintained in the presence of a high gastric acidity and even actual healing of the defect occurred under acid conditions. Ulcer pains may be due to vascular spasm, which may be inhibited by histamine.

B. R. Adolph, Jr.

SURGERY

COPPLESON, V. M.: *Penicillin in abdominal surgery, with special reference to its intraperitoneal use.* (Med. J. Australia., Sept. 6, 1947, V. 2, No. 10, 292-298).

Increasingly, opinion is changing from a negative to a positive attitude with respect to the use of penicillin in abdominal surgery, particularly as given intraperitoneally in combination with its intravenous use and in association with sulfonamides. In experimental peritonitis, with and without intestinal obstruction, the use of penicillin has turned the balance toward recovery, whereas without its use, mortality was nearly 100 per cent. The author has been placing 200,000 units of dry penicillin in the abdominal cavity before closure, as a routine method in abdominal surgery and finds the practice very beneficial, particularly in operations of the biliary tract. Pre-operative and post-operative administration of penicillin also is employed.

Theron, P.: *Surgical aspects of amoebiasis.* (Brit. Med. J., July 26, 1947, 123-126).

The high carrier rate of *E. histolytica* among re-

patriated Service personnel is emphasized in relation to probable effects on post-war civilian practice. Some of the surgical aspects of amoebiasis are discussed on the basis of experience gained in the treatment of African patients. The results are given in a series of cases which include infection of the liver, perforation of the colon, acute infection of the caecum, and intestinal obstruction due to amoeboma.

Love, R. J. M.: *Diathermy dissection of the gallbladder.* (Brit. Med. J., July 5, 1947, 11-13).

When cholecystectomy is performed diathermy dissection of the gall-bladder is the method of choice. In the large majority of cases this is a simple and safe procedure, and the dry abdomen can be closed without drainage, with the great advantage that subphrenic irritation and consequent spasm of the diaphragm are reduced to a minimum. As compared with the standard operation, chest complications and pulmonary embolism are much less common — a fact which is reflected in the lower mortality and reduced morbidity. The technique and value of choledochography are discussed, and a summary is presented of some of the causes of post-operative persistence or recurrence of symptoms.

PHYSIOLOGY

Clark, B. B.: *The effect of syntropan, demerol and trasentine on gastric secretion.* (Federation Proc., V. 6, p. 317, March 1947).

The effects of syntropan, demerol, trasentine and scopolamine were compared with atropine, using the Cope gastric pouch dog. The drugs were administered intramuscularly and the effects observed over a period of nine hours.

The threshold doses were: atropine, 0.001 to 0.002 mg. per kilogram body weight, syntropan, 2.5 mg., demerol 2.5 mg., and trasentine 3.5 mg. At the 5 mg. per kilogram level, the depression in acid production was 40 per cent for syntropan, 45 per cent for demerol and 20 per cent for trasentine. To depress acid production to this extent only 0.002 to 0.005 mg. of atropine was required. The volume of secretion was depressed approximately in parallel with the acid.

I. M. Théone

MacLachlan, P. L., Sleeth, C.K. and Gover, J.: *Effect of anoxic anoxia on bile secretion in the rat.* (Proc. Soc. Exp. Biol. Med., V. 66, p. 275. Oct. 1947).

In order to test the hypothesis that a decrease in bile salt excretion may be responsible for the decreased

rate of fat absorption from the intestine of rats under conditions of low O_2 tension, the authors used rats with bile fistula made according to the technique of Harrington, Greaves, and Schmidt with anastomosis of the bile duct to the vas deferens.

The rats were exposed to a simulated altitude of 24,000 ft. (63 mm. O_2 tension) for 1 four hour period a week. Urine was collected during both low and normal pressure periods and analyzed for bile salts. The absolute amount of bile salts excreted during low pressure periods varied very little from that obtained during control periods. The urine output was significantly increased during periods of anoxia.

J. S. Moffitt

PATHOLOGY

HILSABECK, J. R., AND HILL, F. C.: *Role of the vagus nerves in experimental cinchophen ulcer.* (Proc. Soc. Exp. Biol. & Med., V. 66, p. 155, Oct. 1947).

Previous workers have shown the efficacy of cinchophen in producing peptic ulcers in dogs and they concluded that an increase in acid secretion by the stomach was the probable cause. The present authors decided to test this hypothesis by feeding cinchophen to dogs having previous transthoracic vagotomy performed.

The vagotomized dogs were divided into two different groups according to the dose of cinchophen used. Of the 15 dogs used, only two failed to develop peptic ulcers and these two had not been given cinchophen for a sufficient period. It is the view of the authors that cinchophen acts not by causing gastric hyperacidity but probably by inactivation of one of the protective mechanisms of the stomach.

J. S. Moffitt

LITTLE, J. M., OGLE, B. C., TEAGLEY, J. D., COYER, D.: *Effect of tetraethylammonium chloride in experimental gastric ulceration in the rat.* (Science, V. 106, p. 448, Nov. 7, 1947).

The procedure of pyloric ligation was used to produce gastric mucous ulcers in the rat. In the treated animals 1 milligram tetraethylammonium chloride was given intramuscularly just prior to the pyloric ligation. Ulceration was not completely prevented. However, on the basis of survival time, perforation, and incidence of ulceration the drug appeared to have a definite beneficial effect.

Two patients with active duodenal ulcers have been treated similarly. The authors conclude that there were "suggestive beneficial results."

M. H. F. Friedman

POCOCK, W. A., AND KARK, W.: *Early rising after operation.* (South African Med. J. V. 21, p. 473, 1947).

A series of 629 patients subjected to abdominal surgery of various types are reviewed with special reference to the influence of early post-operative rising on wound healing and the general welfare of the patient. Early ambulation was found to reduce the incidence of vascular complications as well as the incidence of post-operative pulmonary complications. Wound healing was not delayed. Wound rupture or herniation was not increased by early bed rising.

G. Klenner

LAHEY, F. H.: *Care of colostomy.* (Lahey Clinic Bull. V. 5, p. 130, 1947).

The correct technique for the patient to live with a colostomy is taught before the patient leaves the hospital. The bowels are regulated so that they move once every three days. At first an irrigation enema is performed every second day but by the third month every third day is adequate. With proper regulation there is no need for a colostomy bag since involuntary evacuation is rare and may be checked by a teaspoonful of paregoric. At no time are laxatives, oils, or cathartics used. Graded diets are recommended, each adjusted to cover a certain post-operative period. By the third month the diet is practically a complete normal meal. It is most important that the patient have confidence in the eventual control over his bowel movements and that the patient be made to realize that uncontrolled movements for the first six months or so are accidents which will gradually disappear.

B. R. Adolph Jr.

LEWIS, I.: *The packing of abdominal incisions in peritonitis.* (Proc. Roy. Soc. Med., Sept. 1947, V. 40, No. 11, 652-654).

In cases of peritonitis of a foul character, Lewis uses a transverse or grid-iron incision in the Murphy area, drains by a rubber tube in the supra-public stab wound, then firmly closes the peritoneum but leaves the rest of the wound open to granulate. He has had good mortality figures, good wound healing and not too delayed a convalescence.

BABCOCK, W. W.: *Lumbar appendicitis.* (Clin. Med. Sept. 1947, V. 54, No. 9, 305-306).

A description of the unusual symptoms produced by an inflamed appendix which lies posteriorly to the cecum, as well as the surgical approach through the loin.

MAJOOR, C. L. H. AND SUREN, T. J. J.: *Gallbladder complications following resection of stomach for peptic ulcer.* (Brit. Med. Jour., July 5, 1947, 8-11).

From a total of 220 extirpations of the gallbladder

and 174 resections of the stomach over a period of 3 1/4 years, it was observed that gallstones occurred on six occasions shortly after a resection. As a result we believe that is necessary, when patients complain of pain after resection, to look for the cause in the gall bladder rather than the anastomosis. Some arguments support the view that the Billroth II type of operation may further the formation of gallstones.

METABOLISM AND NUTRITION

HENLEY, W. E.: *Diabetes and pregnancy*. (New Zealand Med. J., October, 1947, V. XLVI, No. 255, 386-397).

The general fetal mortality rate in cases of diabetes and pregnancy is from 36.6 per cent to 55 per cent, although in some American clinics following the institution of hormonal replacement therapy (chorionic steroids) the fetal mortality rate is below 10 per cent.

MITRA, K., AND RAD, K. K. P. N.: *Investigations into an outbreak of epidemic dropsy*. (J. Indian Med. Assn., June 1947, V. 16, No. 9, 303-306).

The authors describe an outbreak among native railway employees characterized by diarrhea and (presumably resulting) edema of the legs. This was traced to mustard oil, a cooking fat, used especially in preparing curried rice. The mustard oil responsible was a batch which had become poisonous, and which gave a positive "argemone oil" reaction with nitric acid. Neither the chemistry of the excitant or the mode of pathogenesis of the edema is discussed. Recovery was prompt on discontinuance of this particular lot of the cooking fat.

AXLEROD, A. R., LOBE, S., ORTEN, J. M. AND MYERS, G. B.: *Insulin resistance*. (Ann. Int. Med., October 1947, V. 27, No. 4, 555-574).

The authors present three cases of diabetes mellitus who exhibited spontaneous development and subsequent spontaneous recession of insulin resistance during a two to three year period of close observation. There was no success in attempting to find the cause of insulin resistance in these three cases. In one of these cases a maximum daily insulin requirement of 2,150 units was reached. Both taurine and stilbestrol were used, but it was felt that the improvement in each case was spontaneous.

MARBLE, A.: *Present day treatment of diabetes in the prevention of degenerative complications*. (J. Arkansas Med. Soc., August, 1947, V. 44, No. 3, 69-73).

The chief cause of death among diabetic patients today, both young and old, is arteriosclerosis in its various manifestations. With only partial control of diabetes, the degenerative complications, chiefly ar-

teriosclerotic, affecting particularly the eyes, heart, kidneys, and peripheral vessels, become evident only after 10, 15 or 20 years of diabetes. The incidence of recognizable arteriosclerosis among patients with onset of diabetes at 15.0 years of age or under, and surviving after 20 years of the disease, may reach as high as 70 per cent. Available evidence indicates that by careful, continuous control of diabetes premature arteriosclerosis may be postponed. Careful treatment consists of preventing glycosuria and significant hyperglycemia in so far as practicable by means of (a) a restricted diet, adequate in all essentials, so designed as to provide normal weight and strength and to avoid obesity; (b) insulin, if necessary, in adequate amounts daily, either as to protamine zinc variety alone or in combination with regular or crystalline insulin; (c) regular physical activity suited to the individual; and (d) education of patients in all features of home management.

FOURMAN, L. P. R.: *Changes in blood phosphate after ingestion of glucose and fructose in sprue*. (Brit. Med. Jour., Sept. 13, 1947, 411-413).

The plasma, cell, and whole-blood changes in inorganic phosphate after the ingestion of glucose and fructose were investigated in five normals and four patients with tropical sprue. Observations were also made on the changes in urinary phosphate excretion, and in some of the cases on the changes in the blood "ester" phosphate.

There is normally a fall in the whole-blood inorganic phosphate after the absorption of both glucose and fructose. It usually affects both plasma and blood cells, but may be limited to either. It is associated with a fall in the blood "ester" phosphate content and is partly due to a passage of phosphate into the tissues. The normal whole-blood inorganic phosphate changes after glucose and fructose were diminished or reversed in some sprue patients, indicating a defective absorption of both these sugars. The plasma inorganic phosphate fall was abnormally small; this may have been due partly to the initially low fasting plasma inorganic phosphate levels found in some of the patients. There was a rise in urinary phosphate excretion in the sprue patients, while normally there is either no change or a fall.

No difference could be demonstrated between the absorption of glucose and fructose in patients suffering from tropical sprue.

MISCELLANEOUS

MORETON, JOHN R.: *Atherosclerosis and alimentary hyperlipemia*. (Science, V. 106, p. 190, Aug. 29, 1947).

The author states that the physical state of lipids is the same in both alimentary lipemia and the sustained hyperlipemic conditions that predispose to rapid and severe atherosclerosis. The size of lipid particles was determined by (1) direct observation and photomicro-

graphy of high power, dark-field preparation, (2) Tyndall effect and nephelometry and (3) high speed centrifugation. The author suggests that atherosclerosis is a result of numerous fatty meals with deposition of lipid particles between the intima and fenestrated or reduplicated elastic membrane. The neutral fats and fatty acids are absorbed easily but the cholesterol and cholesterol esters remain as residue.

M. H. F. Friedman

KUSHNICK, T., RANGLES, C. I., GRAY, C. T. AND BIRKELAND, J. M.: *Variants of escherichia coli, pseudomonas aeruginosa, and bacillus subtilis requiring streptomycin.* (Science, V. 106, p. 587, Dec. 12, 1947).

Strains of *Escherichia coli*, *Pseudomonas aeruginosa* and *Bacillus subtilis* that had become resistant to streptomycin were grown on synthetic media. Better and more rapid growth were shown when streptomycin was added. When glucose was present in the medium, the addition of the antibiotic stimulated the growth of all the organisms. The need for streptomycin for reproduction was shown by these organisms only by *in vitro* studies; no *in vivo* studies are reported. However, the authors cite other investigators who found a meningococcus variant to require streptomycin for growth *in vivo*.

M. H. F. Friedman

ASHWORTH, M. A., AND HAIST, R. C.: *A study of the blood flow to liver in relation to carbohydrate tolerance.* (Proceed. Canad. Physiol. Soc., V. 11, p. 3, Oct. 1947).

Blood flow rates and blood pressures were measured in different vessels of the hepatic system. Restricting blood flow through the portal vein resulted in im-

paired glucose tolerance. When the portal vein was anastomosed to the inferior vena cava portal vein restriction had no influence on glucose tolerance. The influence of portal vein blood flow on the sugar tolerance was found to be associated with the systemic arterial blood pressure and the total blood flow to the liver. When there were no alterations in these factors the glucose tolerance was not affected by portal vein constriction.

D. A. Wocker

OWEN-LLOYD, E. AND ROBERTS, D.: *Congenital defect of left diaphragm with volvulus of stomach and transposition of viscera.* (Brit. Med. Journ., Sept. 27, 1947, 485-487).

An interesting and unusual, if not unique, case is described in which examination revealed a congenital defect in the left side of the diaphragm, the presence of the colon in the thoracic cavity. While the case was being studied, an unexplained volvulus of the stomach developed, placing the stomach in the thoracic cavity and returning the colon to the abdominal cavity. Death resulted. The patient was a male infant, eight weeks old.

SHEARER, F. E.: *Organic causes of vomiting during the first six months of life.* (J. Arkansas Med. Soc. Oct. 1947, V. 44, No. 5, 122-124).

Whenever we are confronted with vomiting in a baby, there are several things which we should consider, namely congenital anomalies, birth injuries, infections, pyloric stenosis, malrotation of the bowel, hernias, and intussusception. In the differential diagnosis, we must consider first age of onset; secondly, presence or absence of febrile-reaction; thirdly, type of vomiting and character of vomitus; fourthly, presence or absence of pain.

The Psychosomatic Aspects of Peptic Ulcer

By

HARRY GAUSS, M.D.

DENVER, COLORADO

THE PSYCHOSOMATIC ASPECTS of peptic ulcer is a recent title for an old concept.

In 1932 Harvey Cushing (1) wrote his classic dissertation on the relationship of the interbrain to peptic ulcer. He stated that high strung persons are particularly susceptible to peptic ulcer, that the ulcers tend to heal and become symptomatically quiescent when the patient is put on mental and physical rest, and that the symptoms are apt to recur when the victim resumes his former tasks and responsibilities.

But even Harvey Cushing disclaimed any pretense of originality to a novel explanation of the pathogenesis of ulcer formation. He pointed out that as early as 1841 Carl Rokitansky (2) in his "Handbuch der pathologischen Anatomie" discussed acute perforating ulcers, hemorrhage and erosions, as well as simple chronic ulcers which he believed were caused by morbid conditions of the vagus nerve causing diseased innervation of the stomach and that this morbid condition was associated with extreme hyperacidity of the gastric juice. This concept certainly makes Rokitansky an up-to-date minute modern in his concept of the pathogenesis of peptic ulcer. His ideas however were unfortunately swept aside by the influence of the cellular minded Virchow (3). Now it appears that Rokitansky was a full century ahead of his time.

In 1845 Schiff (4) pointed out that there were vasoconstrictor and vasodilator fibers to the stomach, that the vasoconstrictor effects passed by way of the coeliac plexus, whereas the flushing effects were produced by stimulation of the vagus. Thus he anticipated the counterbalancing of the sympathetic and the parasympathetic systems for the control of the digestive system, and that both of these were under the domination of the higher cerebral centers.

Cushing believed that these centers were located in the interbrain or diencephalon which he considered to be the seat of the primitive emotions. In this view he follows the teachings of Pavlov (5).

Cushing was stimulated to reexamine the current existing concepts of peptic ulcer by his unfortunate experience in losing three patients from perforation of the upper gastrointestinal tract following apparently successful operation for tumors of the cerebellum. It was this experience which prompted him to develop his concept of the neurogenic origin of peptic ulcer. He further expressed the view that psychic

influences can upset the normal sympathetic-parasympathetic balance of the digestive tract in such a way as to give preponderance to the influence of the parasympathetics with an over-preponderance of vagal activity resulting in an irritative lesion of the upper gastrointestinal tract resulting in ulcer, hemorrhage, perforation, etc.

However, even Cushing and Rokitansky were not the first to postulate the neurogenic origin of gastric disturbances; for as far back as 1790, Comparetti (6) wrote an excellent description of the nervous influences on the digestive processes; and it is quite probable that long before him physicians were fully aware of the psychic processes on gastric function.

Within the past decade, the psychosomatic aspects of peptic ulcer has gained in popularity, and the neurogenic views of Cushing, Rokitansky and others have been elaborated to include psychic factors, thus stressing the importance of the higher cerebral functions, namely, those participating in the psychic processes such as fear, anxiety, frustration etc. in the pathogenesis of peptic ulcer.

Peptic ulcer is one of the outstanding medical problems of the world today. In mortality it ranks tenth as a cause of death in this country, while economically it ranks twelfth as a cause of absenteeism from work. It has been estimated that there are approximately 1.5 million people in the United States above the age of thirty in whom peptic ulcers develop during a ten year period.

In the past hundred years, the general incidence of peptic ulcer seems to have been stabilized at about five per cent as judged by necropsy reports, although there has been a distinct shifting in incidence from gastric to duodenal ulcer. Today there are twelve times as many duodenal ulcers as gastric ulcers according to Eusterman and Balfour (7).

Peptic ulcer is primarily a disease of the white collar strata of society. It occurs among persons who live a high tension life, the hard driving, intelligent, alert individuals. It occurs among professional people as doctors, lawyers, musicians, theatrical folk, business executives and others who live and work under great pressure. It has been aptly called "the wound stripe of civilization."

Under the psychosomatic concept of peptic ulcer the exciting factor of the disease is the stress and strain of life, the unfavorable reactions to the environment, economic maladjustment, financial uncertainties, domestic uncertainties, social upheavals, impending calamities, frustrations of any origin, in fact any of a hundred causes that threaten to disturb

the peace and equanimity of a well ordered life or threaten to impede the achievement of a desired goal.

The late World War II provided opportunity to study the relationship of the stress of war to the incidence of ulcer in light of the present concept of the psychosomatic aspects of peptic ulcer.

Berk and Frediani (8) writing of their experience with peptic ulcer among military personnel state that it is extremely common among soldiers; that about three per cent of all admissions in an army general hospital are peptic ulcer, but among the digestive complaints it is extremely high. In their analysis of 841 patients admitted to the Gastrointestinal Section of Tilton General Hospital forty per cent had peptic ulcer. This observation is in keeping with the experience of other U. S. Army General Hospitals and approximates the experiences of other countries. The incidence reported from England is fifty-five per cent of all cases of dyspepsia and thirty-three per cent reported by the Germans.

It is the opinion of most military writers that the military service did not cause the ulcer, rather it activated it. In over ninety per cent, military personnel with peptic ulcer are reported to have had symptoms prior to their entry into military service. In the activation of the ulcer syndrome among soldiers, Berk and Frediani consider the most important fact to be reckoned with is the psychosomatic element. In many of the military persons studied there was a remarkable coincidence between the onset of the distress and some unpleasant episode. Some patients were allegedly asymptomatic until the day they appeared before the induction board. Others were free of distress until after the first meal eaten in the reception center. A few were without difficulty until the poor quality of their work made it appear unlikely that they would qualify for an officer's commission. Further they observed a remarkable recession of previously refractory distress in some patients when their discharge from the army seemed assured and conversely there occurred a recrudescence of distress often with added symptoms in patients who were informed that they would be returned to military duty. They concluded that the psychosomatic aspects of peptic ulcer are outstanding among military personnel and that the influence of anxiety tension and emotional unrest are unmistakable.

The experimental physiologist has added much knowledge to the underlying mechanism of peptic ulcer. Research investigators have succeeded in producing an upper intestinal or jejunal ulcer which resembles human duodenal ulcer both grossly and microscopically. Two methods for producing this type of jejunal ulcer have been developed. One is by the Mann-Williamson operation (9), which consists in performing a gastrojejunostomy in such a manner that the alkaline secretions of the upper intestinal tract are diverted to the distal ileum. In this manner the jejunal mucosa is deprived of the neutralizing effect

of the alkaline secretions and so receives the highly acid gastric juice unmodified by the bile and pancreatic secretions which are alkaline in character. In these so called Mann-Williamson dogs or M - W dogs as they are commonly referred to, jejunal ulcers occur in about 98 per cent of the experimental animals in about two to four months after the short-circuiting of the alkaline juices of the upper jejunum to the distal ileum. The ulcers thus produced are similar to duodenal and jejunal ulcers which occur spontaneously in man. The M - W ulcer is chronic and intractable and unless adequate treatment is instituted results in death almost invariably.

Wangensteen (10) and his associates have produced ulcers in many experimental animals by implanting pellets of histamine mixed with beeswax into the muscle or subcutaneous tissue of the animal. This results in a slow constant liberation of histamine which provokes a long continued secretion of gastric juice which produced jejunal ulcers similar to those of the M - W dogs.

Whenever the acid secretion has been made excessive and continuous in experimental animals, the defensive mechanism is overcome and ulcer is produced. Thus it has been demonstrated by both methods that pure gastric juice alone can destroy and digest living and previously unaltered mucosa of the stomach, duodenum and jejunum producing ulcers which appear identical with peptic ulcers found in man.

If gastric juice alone can produce peptic-like ulcers, then why does not everybody have them? Because Nature has provided a defensive mechanism against them. The defensive mechanism against ulcer formation is multiple in character and consists of at least four factors; (1) Food, which is the normal stimulus to gastric secretion is also the chief factor in protecting the gastric and duodenal mucosa physically against the corrosive action of the acid; (2) mucus likewise acts protectively by coating the vulnerable mucosa, also it acts chemically by rendering buffer action against acid erosion; (3) the intestinal juices act chemically. By being alkaline they neutralize the acid contents. These intestinal juices include principally the pancreatic juice, the duodenal juice and the bile; finally (4) there are the humoral substances which act through the blood stream. They possess the ability to depress and inhibit gastric secretion. These humoral substances have been isolated from the duodenal mucosa and from the urine. The intestinal extract is called enterogastrone. Ivy has demonstrated its effectiveness by injecting it intravenously into M - W dogs. He states that he has been able by this method to protect seventy-five per cent of dogs which otherwise would have developed jejunal ulcers. The urinary extract called urogastrone has a similar action. Sandweiss (11) calls his urinary extract, anthelone.

Up to the present century it was generally believed that the stomach was in a state of rest and secreted no gastric juice in the absence of food or psychic stimuli. This view followed the teaching of Beau-

mont and Pavlov. However, Carlson (12) demonstrated this view to be incorrect and that there occurs a more or less continuous secretion of gastric juice even in the absence of food or evident psychic stimuli, and that this secretion occurs both during the day and night.

In addition to this constant basic secretion, there occurs every two or three hours a transitory phase of hyperemia associated with hypersecretion and increased production of acid gastric juice, also increased hypermotility. This transitory phase lasts twenty to thirty minutes. Increased secretion of acid juice is always accompanied by hyperemia and hyperemia always indicates hypersecretion according to Wolf and Wolff.

These secretions of acid contents are further increased periodically by the presence of food, or the psychic processes of seeing, smelling, tasting of palatable food, as well as the emotional psychic states such as frustration etc.

Carlson states that this stimulation of gastric juice in response to psychic stimuli is a conditioned reflex, and Pavlov has demonstrated that the vagus nerve is the sole efferent pathway for this reflex; further that when these nerves are cut the stimulating effect of appetite on the secretory processes is abolished.

A recent outstanding contribution to the knowledge of peptic ulcer has been made by Wolf and Wolff (13) by their studies on human gastric function made on a man with gastric fistula. There have been three such outstanding studies made. The first was made by the immortal Beaumont on his famous Alexis St. Martin in the early part of the nineteenth century. Beaumont was concerned primarily with the chemistry of digestion. A century later Carlson at the University of Chicago made a similar study with particular reference to the mechanism of hunger and appetite. Recently Wolf and Wolff added their contribution to the study of gastric behavior in which they extended the study to include the aspects of human gastric function. They studied the influence of emotional states on gastric behavior and activity.

They demonstrated that frustration and repressed conflict were associated with hyperemia, increased motility and hypersecretion, that engorgement of the mucosa is associated with lessened resistance to trauma which has an important bearing in the causation of ulcer. They further pointed out that there occurs spontaneously periodically phases of hyperemia, hypermotility and hypersecretion every two or three hours lasting twenty to thirty minutes. Furthermore when a person experiences fear and sadness, it results in ischemia of the mucosa and resultant decrease in the acid secretion; whereas hostility, anxiety, and resentment are accompanied by hyperemia, hypermotility and hypersecretion. They further demonstrated that sustained emotional conflicts are associated with increased severity and duration of the hyperemia, hypermotility and hypersecretion; and that under these circumstances the slightest trauma results in hemorrhage and erosions. Vigorous contractions sometimes

cause pinpoint hemorrhages, also contact of gastric juice on mucosa containing small erosions accelerate the secretion of acid and intensified the engorgement. Thus they established that emotional conflicts cause overactivity of the stomach which results in increased acid activity and this in turn may cause increased motility and hyperemia and so initiate a vicious cycle which may culminate in ulcer formation. By their observation Wolf and Wolff have demonstrated that psychic impulses can produce the same hyperemia and hypersecretion as can be produced by histamine implantation in experimental animals which is one of the experimental ways of producing jejunal ulcer.

The total volume of gastric juice secreted in twenty four hours in man is about 2500 cc; and of this, one fourth to one half is secreted during the night.

Thus, according to Dragstedt (14), it would appear from a consideration of experimental data, that an excessive continuous secretion of gastric juice of normal composition in the empty stomach where the buffering effects of food is lacking presents exactly the situation for the formation of ulcer or the aggravation of an ulcer already existing. Dragstedt reports on his observations of the nocturnal acid of ulcer patients. He states that it is approximately 1200 cc. If this could be reduced then the principle factor which operates in the formation of ulcer would be proportionally eradicated. This led him to develop his concept of supra-diaphragmatic vagotomy or complete section of both vagus nerves as a form of treatment for ulcer of the stomach. In this manner he removes the pathway for secretory stimulation and so reduces the acid secretion of the stomach. Dragstedt claims that by this method he has reduced the nocturnal acid of ulcer patients by as much as fifty per cent, or from approximately 1200 cc. to about 500 cc. according to his 1944 report in "Gastroenterology."

He states that "relief of the ulcer distress has been uniform, persistent and very striking. It occurred immediately and within a few days after the operation."

By his observation, Dragstedt has made one of the significant contributions to the knowledge of the physiology of gastric behavior and the nature of peptic ulcer. The time, however, is too short to evaluate fully the significance of his operation. More data is needed and more time must elapse before the full significance of his operation can be arrived at. Dragstedt is very modest in his claims for the indications of his operation. He does not recommend it as a panacea for the treatment of all forms of ulcer or for simple uncomplicated ulcer. He states specifically that "this procedure will find a place in the treatment of intractable peptic ulcer." Further it is not a totally complete form of treatment and that "judicious management should supplement surgery."

The operation of vagotomy has aroused a tremendous amount of interest in the surgical treatment of peptic ulcer. The reports from this operation are glowing and inspiring. Ruffin (15) and his associates report on their thirty vagotomies performed at Duke

Hospital. They state "since vagotomy, every patient has been relieved of ulcer symptoms and has been able to consume a full and unrestricted diet without ill effects."

Moore (16) and his associates report their experience with forty cases of vagotomy over a two year period. They state that the clinical results are good, that healing of the ulcer generally takes place; further there occurs an early decrease in the fasting acidity and motility which returns to normal within a year. They suggest that the immediate relief of pain and healing of the ulcer is probably due to changes in the fasting stage of motility and secretion. These changes however are transient and the prolonged relief must be due to some more subtle effect probably traceable to severance of those nervous pathways which communicate the patient's adaptive reactions from the brain to the stomach. Undesirable side effects however occurred in about ten per cent of the patients.

Yet vagotomy is not without its dangers and mortality. Weeks, Ryan and Van Hoy (17) report two deaths following supradiaphragmatic vagotomy. The Journal of the American Medical Association on January 18, 1947 cautions editorially that "the period of observation has been too short to permit a final evaluation of the method, and the question of ultimate regeneration of the divided vagi remains undecided. Such complications as dilations of the stomach and greatly impaired motility make necessary delay in the final conclusions regarding the exact value of the technique." Winkelstein (18) cautions that "the abolition of the parasympathetic innervation of the pancreas, biliary tract, kidneys and small intestines may ultimately lead to harmful effects."

Grimson (19) and his associates report their experience with transthoracic vagotomy in fifty-seven patients with peptic ulcer. They state that although healing or quiescence of duodenal or gastric ulcer has followed transthoracic vagotomy alone, nevertheless disturbances in gastrointestinal function have occurred, such as gastric obstruction and gastric retention. They are of the opinion that vagotomy alone should not be used as a standard treatment for all duodenal or gastric ulcers which are resistant to medical management.

Recently we have encountered an instance of marked gastric retention and severe protracted diarrhea following transthoracic vagotomy. Patient B. Z., an American of Italian extraction, had a transthoracic vagotomy performed in January 1947 for duodenal ulcer of many years standing. He had an uneventful convalescence and for several weeks afterwards he felt quite good and was free of all abdominal distress; then he began to develop nausea, cramps and diarrhea. He had from five to fifteen stools a day associated with marked cramps. The stools were liquid in character and contained visible blood at times. This kept up from February 1947 to July 1947 without relief. He lost about twenty pounds,

became tired and weak and unable to work at his business of an electrical contractor so that he was compelled to close his business because of his inability to attend to his obligations. He stated that his stomach felt fine, he had no trouble there whatsoever, but it was the annoying cramps and diarrhea which troubled him and interfered with his ability to work. The dysentery occurred day and night and this interfered with his sleep and rest.

Our examination made in July 1947 showed an emaciated anemic, white, adult male 39 years old in a highly emotional state. He weighed 132 pounds measured five feet eight inches in height, his pulse was 100, his temperature was 97.4, his respiration was 16, his blood pressure was 100/64.

He had an extensive surgical scar in the left lower thoracic region. The chest examination was otherwise within normal limits except for the tachycardia. In the abdomen there was diffuse muscle spasm, diffuse tenderness in the lower abdomen, the descending colon was spastic, palpable and tender. The reflexes were present, equal and exaggerated. The Ewald test meal at 60 minutes showed a free acid of 10 and a total acid of 30. The blood showed a secondary anemia, the urine was normal. Proctoscopic examination showed a reddened, edematous, swollen mucosa containing multiple small ulcerated areas which bled easily, and which conformed to the type encountered in the so-called idiopathic ulcerative colitis. A scraping from the mucosal wall of the sigmoidal colon showed some blood, numerous white blood cells, debris, but no parasites or common pathogenic organisms.

An X-ray of the stomach showed it to be of the fishhook type of normal size with markedly active peristalsis and without defects. The cap however was persistently defective and deformed and of increased tonicity and at no time did it fill well. At six hours there was a marked gastric retention, with the head of the barium meal in the descending colon, the colon was markedly spastic and irritable. At twenty-four hours there remained a marked gastric retention of approximately one third of the barium meal, while the colon had almost completely evacuated its barium contents, with only a few scattered small spots remaining. A barium enema was given at this time. The colon filled throughout its entire length, but it was markedly irritable, spastic and hypertonic throughout its entire length. The injection was painful and disagreeable to the patient who experienced cramps and had trouble in retaining the injection. A diagnosis was made of Transthoracic Vagotomy, Old Duodenal Ulcer, 24 Hour Gastric retention, Chronic Functional Diarrhea.

Treatment was prescribed symptomatically consisting of a bland diet, antispasmodics, sedatives, sulfathiazol suppositories. Under this program the patient began to improve slowly but consistently. In the second month of treatment, his diarrhea had subsided so that he now had from one to three formed



Figure 1 — Twenty-four hour barium meal study in patient B. Z. six months after vagotomy showing marked gastric retention and marked irritability of the colon. The colon has almost completely evacuated its contents. The patient suffered from chronic diarrhea and had from 5 to 15 stools daily.

stools in twenty-four hours, the cramps had subsided, he gained fifteen pounds and was able to return to work.

It is ironic that Dragstedt's work which has been so instrumental in establishing the psychosomatic aspects of peptic ulcer, may likewise encounter some of its opposition from the same direction.

As the writer sees it, this operation is a procedure for short circuiting the stomach out of the emotional life of the patient. That is fine as far as it goes. But what of the emotions that remain to be disposed of somehow in the body? Even with the stomach short circuited out, the emotions remain to plague the victim, although the stomach no longer responds to them. There remains nevertheless the fundamental psychiatric principle of organ language which hypothesizes that if an outlet cannot be found for emotional tension, then the body will find a means of expressing this tension through a kind of organ language. It so happens that the gastrointestinal tract is above all the pathway through which emotions are most often expressed in organ behavior. Because the gastrointestinal tract is the oldest system in the body phylogenetically, it is most likely to be used to express those emotions which cannot be conveyed through regular channels. When the stomach is short circuited out of the emotional life of the patient the principle of organ language remains nevertheless. If the stomach will not express the emotional conflict, then some



Figure 2 — Barium enema study in patient B. Z. 6 months after vagotomy showing marked gastric retention at twenty-four hours and marked colon irritability in its entire length. Injection of the enema was disagreeable and caused cramps.

other organ will take up the burden. Since the circulatory system is the second system in frequency to express emotional conflicts, we can look for an increase in circulatory disorders, as well as that in other systems in these patients on purely theoretical lines. Indeed Chester Jones (20) has already reported one patient who died of a cerebral vascular accident six months after vagotomy.

Clinical psychiatry has as its main function the task of teaching people to live within the safe limits of their nervous system; cardiology attempts to teach people to live within their cardiac reserve; clinical metabolism teaches diabetics to live within their carbohydrate tolerance; so why should clinical gastroenterology not attempt to teach ulcer patients to live a restricted emotional life, one that is compatible with a normally functioning digestive tract, so that their digestive tracts will not be called upon to penalize itself in vicariously expressing those emotional reactions which it was never intended to do in the first place.

Alvarez (21) voices this same thought when he advocates that ulcer patients should lead the "calm life." Some of us have been recommending this as a therapeutic principle to our patients for years.

Every ulcer patient coming to us is subjected to a psychiatric analysis. This procedure follows established psychiatric principles. At times this analysis

is surprisingly simple, at other times it is difficult. If the emotional life is too involved, the services of a trained psychiatrist are made use of. The patient's emotional stresses are ferreted out and he is advised to correct them. Here again the solution may be simple or it may be difficult. It may be necessary at times to go so far as to advise the patient to seek a change of work, to quit trying to keep up with the Joneses to quit trying to be a square peg in a round hole, and at times a change of family relationship is indicated. As we see it this is sound clinical practice both from psychiatric and gastroenterologic points of view.

We employ of course all the other established therapeutic principles of ulcer treatment as bland diet, antacids, aluminum hydroxide gel, magnesium trisilicate, antispasmodics, sedatives, rest, vacations, etc.

We believe that there are other factors involved than the emotional stresses which contribute to the pathogenesis of ulcer, such as focal infection, excessive use of tobacco, excessive use of tea and coffee, excessive use of alcohol, and some other factors. These are given consideration in the management of the individual patient.

To assist in the program of relaxation for the patient with a psychic conflict or emotional stress we like to employ a prescription containing Sodium Phenobarbital 20 grs., Gelusil 8 oz., and Oil of Peppermint 3 gtt. with instructions to take a teaspoonful two hours after meals and as directed. We employ this prescription for a variable period, sometimes for several months or even longer if indicated.

Employing these principles, the majority of our patients are symptom free in a very short period of time, sometimes within forty-eight hours and remain so for long periods of time, or until they kick over the traces.

The use of barbiturates is justified on the basis of their well known pharmacologic action on the central nervous system, where they effect a depressant action to produce a sense of calmness. It has been established that the barbiturates tend to decrease the general tonus of the digestive musculature and the amplitude of the rhythmic contractions as measured in experimental animals. Tournade and Joltrain (22) found that epival, a form of barbiturate, checked the stimulating effect of the vagus nerve so that under barbiturate it failed to produce its characteristic effects on the intestine. Goodman and Gilman (23) state that the therapeutic effects of barbiturates in the relief of symptoms arising from the gastrointestinal tract are attributable to depressant action on the central nervous system.

The use of barbiturates to reduce the irritability of the digestive tract and produce a state of calmness is in line with its widespread use in cardiac disorders, hypertension, coronary insufficiency and coronary sclerosis where it is likewise employed for the same

reasons to reduce nerve tension and allay apprehension.

There are of course a group of patients who just do not respond to this program, some who will not cooperate, some will not lead the "calm life," some who resist psychiatric adjustment, and some who cannot make the adjustment, together with some others they form a group of intractable cases in whom the medical management cannot be said to be successful. Winkelstein recognizes the existence of this group of intractable ulcer patients when he states that about seventy-five per cent of ulcer patients react favorably to medical management and do not require surgical therapy, while about twenty-five per cent are refractory and may require surgical therapy.

The problem of peptic ulcer cannot be considered to be a closed subject in any sense of the word at the present. Since the specific cause of ulcer is still a debatable subject, all existing forms of treatment must be considered palliative at best. Yet almost every year we are fed some new "cure," some magical injection, some new wonderful form of nutriment and again that "operation of choice." Each of these merit serious consideration, sober judgement, and proper evaluation devoid of rash enthusiasm. Only recently a solution of L-histidine monohydrochloride was highly exploited as the magical injection which would cure ulcers. On closer study it was found to have the therapeutic effects of distilled water. The recently formed National Committee of the American Gastroenterological Association for the Study of Peptic Ulcer will serve as a clearing house for the collecting, integrating, and evaluation of data on matters relating to peptic ulcer.

A fairly recent development in ulcer therapy is a humoral substance or autocoid called enterogastrone (24) prepared from the intestinal mucosa in the presence of adequate concentrations of fat and sugar in the intestinal chyme. Enterogastrone has been shown to have the specific properties of inhibiting gastric secretion and motility. Ivy has shown that this substance when given parenterally inhibits or abolishes the gastric secretory response to histamine. This substance has been shown to protect M-W dogs from development of jejunal ulcers, and clinical trial gives great promise. Twenty-four of a series of thirty-two patients have been asymptomatic for an appreciable period of time. Enterogastrone is the closest thing developed so far that approaches a specific treatment for peptic ulcer. Ivy has pointed out that it is reasonable to suppose that future studies will develop some method for increasing the resistance of the mucosa to injury and for blocking the acid secreting properties of the parietal cells of the stomach. When that is done we may have a specific cure for peptic ulcer. Until then all existing forms of treatment are palliative only and must be considered so before waxing unduly enthusiastic about them.

SUMMARY

Within the past decade, the psychosomatic as-

pects of peptic ulcer have gained a place of importance in the pathogenesis of this disease. The older neurogenic view of Rokitsky and Cushing have been elaborated to include the psychosomatic factors of fear, anxiety, frustration and other emotional states in the causation of peptic ulcer.

Some writers of World War II have observed that the psychosomatic factors as emotional unrest and the anxiety state were prominent factors in the pathogenesis of peptic ulcer among military personnel.

Experimental physiology has greatly aided the study of peptic ulcer by producing upper intestinal or jejunal ulcer by the Mann-Williamson operation. These jejunal ulcers in the so called M-W dogs have many of the characteristics of human peptic ulcer, and if untreated, the animals die. It has been demonstrated in these M-W dogs that unbuffered hyperacidity alone will cause jejunal ulcer.

It has been demonstrated by Wolf and Wolff that the emotional states as frustration and repressed conflict result in hyperemia, increased motility, hypersecretion and hyperacidity of the gastric mucosa in a human subject with a permanent gastric fistula, further that this induced engorgement is associated with decreased resistance to trauma which has an important bearing on the causation of ulcer. Hostility, anxiety and resentment and sustained emotional conflict caused increased hyperemia, hyperacidity, hypermotility and hypersecretion, and that under these circumstances, the slightest trauma caused hemorrhage and erosions which lead to ulcer formation.

Dragstedt has developed his operation for supradiaphragmatic vagotomy which aims to reduce the pathway for secretory stimulation of acid into the stomach and so remove a primary cause for the formation of ulcer.

As the writer sees it this operation is a procedure for short circuiting the stomach out of the emotional life of the patient. But what of the emotions that remain to plague the victim? True, the stomach no longer responds to the emotional excitation for it has ceased to be the alarm bell of emotional stress, there remains nevertheless the fundamental psychiatric principle of organ language which hypothesizes that if an outlet cannot be found for emotional tension, then the body will find a means of expressing this tension through a kind of organ language. Hence in patients with vagotomy, we can look for an increase in the incidence of circulatory disease, endocrine disorders, allergy disturbances as well as other disorders which respond to impulses of the autonomic nervous system.

For many years we have been fed a new "cure" for peptic ulcer periodically. Some of these wonderful "cures" consist of shots, some are wonderful forms of nutriment, some are that "operation of choice," etc.

The closest approach to a specific treatment for peptic ulcer so far developed is the recent development of the autocoid enterogastrone which has the specific properties of inhibiting gastric secretion and motility. Unfortunately, enterogastrone is still in the experimental stage.

Until enterogastrone or some other substance with specific properties to inhibit gastric secretion and motility is developed to a higher degree of therapeutic practicability, all existing forms of treatment for peptic ulcer are palliative and should be considered as such.

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The Effect of Salicylate Medication upon the Urinary Excretion of Vitamin C

By

J. M. SPITZER, M.D.

and

SHEPARD SHAPIRO, M.D.

NEW YORK, N. Y.

THE QUANTITY of vitamin C excreted in the urine under ordinary nutritional conditions is meager. Normally, this becomes increased only after large amounts are ingested and the body stores saturated (1). It has been reported that the urinary excretion of ascorbic acid can be increased by the ingestion of salicylate, particularly in children (2). In adults, however, this is believed not to occur (3,4).

Studies of the effects of salicylate medication upon the blood coagulation mechanism have demonstrated a prothrombinopenia-inducing activity (5), (6). Because of the possible role of vitamin C in this system, at least as it concerns capillary wall integrity in rheumatic fever, in which salicylates are used freely and in considerable quantity, the study has been extended to learn the conditions under which salicylate influences the urinary excretion of vitamin C. Guinea pigs, children and adults were used in the present investigation.

The experiments were begun with guinea pigs because it was thought that conditions could be controlled more carefully than with human subjects. Two guinea pigs of approximately 400 grams weight were maintained in individual cages. The cages were lined at the bottom with a fine mesh wire gauze and above this a coarser one which retained the feces. Water was supplied by means of an inverted bottle with a tube protruding into the cage through the wire gauze lid. The cages were mounted so that the urine was filtered through a fine wire gauze over a beaker which in turn was inserted into a Dewar flask containing "dry ice." The beaker contained some 20% metaphosphoric acid as an additional precaution against loss of ascorbic acid. Urines were titrated daily with 2:6 dichlorophenol indophenol on an aliquot of 4 ml. and the 24 hour quantity was calculated

from this. The 2:6 dichlorophenol was standardized against a dilute known solution of ascorbic acid made from a more concentrated one which had been standardized by titration with 0.0095 N iodine which in turn had been standardized against a thiosulfate solution of known concentration as obtained with potassium biiodate. The dye solution was checked frequently. Made up to contain 40 mg. (plus 80 mg. sodium bicarbonate) in 200 ml. water as recommended by Van Eckelen and Heinemann (7), it was found to keep very well. The vitamin C solutions used as standards were prepared in 5% metaphosphoric acid and kept in the refrigerator. Both in the case of the guinea pig urines and human urines, treatment with barium acetate to remove non-vitamin C reducing substances yielded only very slightly lower titration values with 2:6 dichlorophenol indophenol.

The diet of the guinea pigs consisted of pellets of compressed oats and grass which had been heated to 165° C. for several hours to destroy completely any ascorbic acid. In addition, each guinea pig received 5 mg. ascorbic acid (synthetic) weighed out daily and placed on a very small piece of lettuce. The guinea pigs consumed this rapidly and completely. This was continued for six days and the elimination of ascorbic acid was determined until the figures appeared sufficiently constant to warrant proceeding with the administration of acetylsalicylic acid. The drug was weighed out daily in 2.0 mg. quantities and also administered orally by placing it on a very small piece of lettuce which was completely consumed. The ascorbic acid excretion was measured and when no increase was observed over the control period, the quantity of acetylsalicylic acid was increased. (The amount given was equivalent in mgms. per guinea pig roughly to 2 to 3 gms. daily, per human adult on a weight basis). For three days following this, the acetylsalicylic acid was given subcutaneously. A slight decrease in vitamin C excretion was observed. The dose was increased to 120 mg. per guinea pig per day. (the equivalent of 12 grams per human adult). This was divided into two parts, one half was given orally, the other subcutaneously. The latter portion

From the Third (New York University) Division Goldwater Memorial Hospital, Welfare Island, New York, N. Y., the Department of Medicine, New York University College of Medicine, New York, N. Y., and Willard Parker Hospital, New York, N. Y.

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TABLE I

(A) Vitamin C excretion by Two Guinea Pigs on a diet of "pellets" and oats, heated at 165°C for two hours. This was supplemented with 5.0 mgm. synthetic vitamin C daily.
(B) The influence of acetyl salicylic acid, orally and subcutaneously administered on the excretion of Vitamin C.

Date	G. P. No. 1	mgm. of Vitamin C excreted	G. P. No. 2	Remarks
2-12-46	0.95		1.08	Heated pellets & oats + 5 mgm. Vitamin C
2-15	0.68		1.23	Heated pellets & oats + 5 mgm. Vitamin C
2-16	0.50	avg. of six days is 0.65	0.79	Heated pellets & oats + 5 mgm. Vitamin C
2-17	0.52		1.65	Heated pellets & oats + 5 mgm. Vitamin C
2-18	0.57		1.51	Heated pellets & oats + 5 mgm. Vitamin C
2-19	0.67		1.13	Heated pellets & oats + 5 mgm. Vitamin C
2-20	0.55		1.01	A above + 20 mgm. acetyl salicylic acid orally
2-21	0.66		1.06	A above + 20 mgm. acetyl salicylic acid orally
2-22	0.68	avg. of six days is 0.59	0.81	A above + 20 mgm. acetyl salicylic acid orally
2-23	0.79		1.23	A above + 20 mgm. acetyl salicylic acid orally
2-24	0.33		1.26	A above + 20 mgm. acetyl salicylic acid orally
2-25	0.55		0.74	A above + 20 mgm. acetyl salicylic acid orally
2-26	0.35		0.70	A above + 20 mgm. Na acetyl salicylic acid subcutan- eously
2-27	0.41	avg. of three days is 0.39	0.75	A above + 20 mgm. Na acetyl salicylic acid subcutan- eously
2-28	0.41		0.77	A above + 20 mgm. Na acetyl salicylic acid subcutan- eously
3-1	0.51		0.74	A above + 60 mgm. Na acetyl salicylic acid subcutan- eously and 60 mgm. acetyl salicylic acid orally
3-2	0.58	avg. of three days is 0.52	0.83	A above + 60 mgm. Na acetyl salicylic acid subcutan- eously and 60 mgm. acetyl salicylic acid orally
3-3	0.48		0.88	A above + 60 mgm. Na acetyl salicylic acid subcutan- eously and 60 mgm. acetyl salicylic acid orally
3-4	0.56	avg. of four days is 0.38	0.87	Heated pellets & oats + 10 mgm. Vitamin C
3-5	0.38		0.86	Heated pellets & oats + 10 mgm. Vitamin C
3-6	0.27		0.76	Heated pellets & oats + 10 mgm. Vitamin C
3-7	0.30		0.67	Heated pellets & oats + 10 mgm. Vitamin C

was neutralized with alkali to make it soluble. This was continued for three days. No increase in the urinary elimination of ascorbic acid was observed.

The urinary excretion of vitamin C in man was studied next. The diet was calculated so that the average intake was 40 mg. of vitamin C daily. Preliminary to the investigation of the larger group one normal adult was studied as follows: Each specimen of urine collected during the day was titrated for its ascorbic acid content directly after voiding. (The subject was a laboratory worker and the determinations were made by him). This was done for seven days and showed values for 24 hour excretions ranging from 18.6 mg. to 24.8 mg., except for a single

day when excretion was only 1.5 mg. Then acetylsalicylic acid was taken in divided doses: 1 g. the first day, 2 g. on each of the next two days. A slight increase occurred but this did not exceed some of the higher control values. When aspirin was then withdrawn the values for ascorbic acid continued to be about equal to the control figures. The aspirin was increased to 3 g. for two days but still change in the quantity of vitamin C excreted in the urine did not occur.

Shortly following this the adult became ill with an acute upper respiratory infection. There was no elevation in temperature but on several occasions the oral temperature fell to the subnormal level of 96.5-

TABLE II

Vitamin C excretion by adult subject during acute upper respiratory infection and salicylate medication

Date	Mg. Vit. C. Excreted	Remarks
4-21	3.8 mg. night spec. 6.6 mg. A. M. spec.	Figures for comparison on control days 4.7 mg. and 2.4 mg. 3.2 mg. and 4.8mg. 5.2 mg. and 4.2 mg. 4.5 mg. and 4.0 mg. Beginning symptoms acute cold. 0.7 gm. aspirin taken just prior to two values given column 2
4-22	52.8	Took 1 g. aspirin. Vitamin C intake 45 mg. Severe cold.
4-23	47	Took 1 g. aspirin Vitamin C intake 45 mg.
4-24	39.8	Cold much improved. Vitamin C intake 45 mg.
4-25	23.8	No symptoms of cold Vitamin C intake 45 mg.

TABLE III

Vitamin C excretion in 12 year old girl before and after aspirin medication and while taking aspirin in presence of acute upper respiratory infection

Date	24 hr. Vit C. Excretion	Remarks
3-22	25.3 mg.	Intake Vitamin C 40 mg.
3-23	20.0	Intake Vitamin C 40 mg.
3-24	26.3	Intake Vitamin C 40 mg.
3-25	24.1	Intake Vitamin C 40 mg. Control
3-26	22.6	Intake Vitamin C 40 mg. Period
3-27	21.3	Intake Vitamin C 40 mg. took 1 gm. aspirin
3-28	25.4	Intake Vitamin C 40 mg. took 1 gm. aspirin
3-29	21.9	40 mg. Vitamin C Intake Control
3-30	19.7	40 mg. Vitamin C Intake Period
3-31	22.5	Vit. C Intake 40 mg. Fever, took aspirin 2 gm. acute cold
4-1	42.	Vitamin C Intake 40 mg. Fever, took aspirin 2 gm. severe symptoms
4-2	112.7	Vitamin C Intake 50 mg. Fever
4-3	54.2	Vitamin C Intake 50 mg. Fever
4-4	56.1	Vitamin C Intake 50 mg. Fever
4-5	21.4	Vitamin C Intake 45 mg. normal temperature
4-6	15.5	Vitamin C Intake 45 mg. normal temperature

97°F. On the first day of the illness 0.6 g. aspirin were taken. Two separate specimens, a night specimen and one the following morning were collected, and titrated in the same manner as described above. The values were the same as those obtained during the control period. The next day 1 g. of aspirin was taken. There was no fever but the vitamin C continued at 40 mg.; a considerable rise over the excretion in the earlier experimental period occurred. The earlier average obtained was 25 mg. per day.

The next day 1 g. of aspirin was again administered. The quantity of vitamin C excreted in the urine was still elevated, 47 mg. The following day aspirin was not taken because the infection had largely subsided. The urinary excretion of ascorbic acid fell to 39.8 mg. and on the following day to 23.8 mg. which is equal to the normal control value for this adult.

An additional group of six adult patients were studied. The procedure was altered to conform with hospital routine. The diet was the regular hospital fare. The vitamin C content was estimated to vary within narrow limits from day to day, the average being 42.5 mg. No medication other than aspirin was taken during the period of study. Urine was collected as 24 hour specimens. To each voided specimen 5 ml. of 5% metaphosphoric acid was added as a preservative. Following a control period of two to seven days aspirin was administered generally in doses of 1 gm. each, four to six times daily, for a minimum of four days and followed by a second control period varying from one to three days during which time no medication was given, and followed by a second control period varying from one to three days.

TABLE IV

CASE NO.	AGE	SEX	DIAGNOSIS	AVERAGE DAILY EXCRETION MG. CONTROL PERIOD	ASPIRIN MEDICATION	VITAMIN C RECOVERY PERIOD	REMARKS
1.	79	M	Pulmonary emphysema	5. days 1.86 mgm.	6/g/d; 10 d. 2.67 mgm.	3 days 2.55 mgm.	Normal temperature
2.	59	M	Rheumatoid Arthritis	5. days 3.79 mgm.	6/g/d; 10 d. 4.54 mgm.	3 days 3.89 mgm.	Normal temperature
3.	31	F	Rheumatic Heart Disease Inactive	3 days 2.05 mgm.	6/g/d; 1 d. 3.12 mgm.	3 days 1.17 mgm.	Aspirin stopped after one day; nausea. Normal temperature
4.	65	M	Diabetes mellitus controlled	7 days 4.94 mgm.	4/g/d; 4 d. 3.27 mgm.	3 days 4.56 mgm.	Normal temperature
5.	54	M	Thromboangitis obliterans	7. days 3.94 mgm.	4/g/d; 4d. 3.98 mgm.	4 days 3.69 mgm.	Normal temperature
6.	35	M	Rheumatic Heart Disease Active	2 days 3.68 mgm.	2/g/d; 1 d. 15.17 mgm. 4/g/d; 4 d. 26.58 mgm.	3 days 10.05 mgm.	Normal temperature

RESULTS

Of the six adults studied only one showed a change in the urinary elimination of Vitamin C following the ingestion of acetylsalicylic acid. During the experiment all six had normal temperature.

The investigation was made also in children. A preliminary study was made in a child (female) 12 years of age. The intake was 40 mg. ascorbic acid daily. Urines were titrated after voiding with as little delay as possible. When the daily output of vitamin C was fairly constant (nine day control period) aspirin was given in doses of 1 gm. on each of two successive days. The daily excretion of vitamin C was slightly increased and this promptly fell to the control values after the aspirin was withdrawn.

The child became ill while the experiment was being made. She developed an acute upper respiratory infection with fever. Aspirin was resumed in doses of 2 gms. on the first and second days. The vitamin C elimination increased sharply. On the first day when aspirin was resumed it was still in the control range. (20-30 mg.) the second day, 42 mg., and on the day following 112 mg. On the fourth day it was 54.2 mg. and on the fifth day 56.1 mg. following which it promptly fell to the control value. It is important to note that on the first day when the child had fever there was no increase in the elimination of vitamin C and that the sharp rise followed the administration of aspirin for at least 24 hours. A group of eleven children recovering from acute contagious diseases were studied in similar fashion. Three showed an increase in the urinary excretion of vitamin C after salicylate

medication. One of these exhibited a marked rise the day following the withdrawal of the aspirin.

DISCUSSION

The above data indicate a variable response in the urinary excretion of vitamin C following the ingestion of salicylates. The guinea pigs yielded no alteration in vitamin C excretion and in man only two out of seven of the adults showed a definite rise in the amount of ascorbic acid eliminated in the urine after the medication. In the children the change was more frequent, nine out of twelve revealing increased excretion after aspirin.

The change, when it occurred, bore no relation to the quantity of salicylate ingested but in every instance in which the urinary excretion of vitamin C became elevated after salicylate medication, virus infection was either active or recent. The augmented elimination of the vitamin occurred independently of the body temperature. The illnesses were the common cold, epidemic parotitis, and rheumatic fever. The present study does not include infections due to bacterial agents, hence we do not know whether the change occurs only in virus diseases. The data indicate clearly that at least in the presence of the viral infections mentioned salicylate therapy may increase the urinary excretion of vitamin C.

The mechanism whereby the change in urinary excretion of ascorbic acid is brought about is not clear. Several possibilities present themselves: 1.) The permeability within the kidney is altered, permitting a freer passage of ascorbic acid into the urine. 2.) Re-absorption through the tubular epithelium is inhibited.

TABLE V

CASE NO.	AGE YRS.	SEX	DIAGNOSIS	AVERAGE DAILY CONTROL PERIOD	EXCRETION MGM. VITAMIN C RECOVERY PERIOD	REMARKS	
1.	4	M	Epidemic Parotitis, recent	3 days 1.42 mgm.	2/g/d; 4 d. 28.53 mgm.	4 days 2.33 mgm.	Normal temperature convalescing
2.	8	M	Epidemic Parotitis, recent	7 days 5.03 mgm.	4/g/d; 4 d. 14.23 mgm.	1 day 4.5 mgm.	T. 102°F. 1st day of control period
3.	5	F	Epidemic Parotitis, recent	3 days 2.1 mgm.	4/g/d; 4 d. 2.1 mgm.	4 days 1.0 mgm.	Normal temperature
4.	4	M	Nasopharyngitis	2 days 1.34 mgm.	2 /g/d; 5 d. 4.05 mgm.	4 days 1.37 mgm.	Normal temp.
5.	4	M	Otitis media acute	1 day 0.77 mgm.	1/g/d; 3 d. 7.1 mgm.	3 days 5.65 mgm.	T. 102°F. one day after aspirin
6.	12	F	Epidemic Parotitis, recent	4 days 1.5 mgm.	4/g/d; 4 d. 1.64 mgm.	3 days 4.47 mgm.	Normal temp. convalescing
7.	6	M	Epidemic Parotitis, recent	2 days 1.32 mgm.	4/g/d; 3 d. 19.15 mgm.	3 days 5.22 mgm.	Normal temp. convalescing
8.	7	F	Observation Parotitis,	4 days 1.39 mgm.	4/g/d; 4 d. 2.38 mgm.	1 day 1.13 mgm.	Normal temp.
9.	5	M	Epidemic Parotitis, recent	4 days 1.7 mgm.	6/g/d; 2 d. 4/g/d; 2 d. 8.5 mgm.	2 days 1.7 mgm.	Normal temp. convalescing
10.	3	M	Cervical Adenitis	4 days 2.07 mgm.	4/g/d; 4 d. 2.36 mgm.	1 day 1.86 mgm.	T. 100.4°F. 1st day control period
11.	3 1/2	M	Epidemic Parotitis, recent	3 days 0.8 mgm.	4/g/d; 4 d. 26.6 mgm.	2 days 0.6 mgm.	Normal temp. convalescing

3.) Salicylate enters into combination with vitamin C and blocks absorption. 4.) Salicylate competes with the tissues for vitamin C.

The phenomenon of increased vitamin C excretion under the conditions described has clinical implications. Hemorrhagic phenomena which may vary in intensity from petechiae to massive bleeding may occur as part of the rheumatic state (8). It is not known what factors are responsible for the maintenance of the capillary wall in a normal state. The findings in scurvy implicate vitamin C in the process. Since salicylates are apt to disturb the urinary excretion of ascorbic acid it becomes evident that the simultaneous administration of the vitamin with

the salicylates is rational therapy. Related to this is the prothrombinopenia-inducing action of salicylates (5) (6). The disturbances in both vitamin C excretion and prothrombin elaboration are susceptible to correction simply by the administration of vitamin C and vitamin K perorally. Therefore, it seems wise to administer these substances simultaneously with salicylates.

CONCLUSION

The primary excretion of vitamin C may be significantly increased following the ingestion of salicylate in the presence of viral infections.

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Leiomyosarcoma of the Stomach with Particular Reference to the Gastroscopic Picture

By

EDDY D. PALMER, CAPT., M.C., USA

WASHINGTON, D. C.

LEIOMYOSARCOMA OF THE STOMACH is a rare tumor. Schindler, Blomquist, Thompson and Pettler (1) have estimated from frequently quoted statistics that carcinoma of the stomach is a thousand times more common, and, although they had treated four cases in a period of only three years, could collect only 94 cases from the literature.

There are reported here the cases of two young soldiers, admitted to this Section on consecutive days, who were found to have leiomyosarcoma of the stomach. This happy coincidence presented the opportunity for simultaneous comparative gastroscopic study of the disease in two patients, before and after the histologic picture was known, and before, during and

after roentgen therapy. The tumor was correctly diagnosed gastroscopically in one case prior to biopsy, on the basis of Schindler's (1) description.

CASE I

This 23 year old white male was admitted to Walter Reed General Hospital 15 November 1946 because of rapid weight loss and dull post-prandial epigastric pain of four months' duration. He was thin and chronically ill. There was no icterus. The abdomen was normal to examination. Laboratory studies showed a moderate anemia, blood in the stools, and absence of free gastric acid on histamine stimulation.

On 16 November the patient was gastroscopied. An obstruction was met at 45 cm. and the instrument was passed no further. Only the fundus and a small portion of the posterior wall were visualized. The former appeared normal. The mucosa was intact over the posterior wall, but was pale and more than usually translucent, although not atrophic. Here there was heavy intramural infil-

Gastrointestinal Section, Walter Reed General Hospital, Washington, D. C.

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tration with absence of rugae, and the lumen of the stomach could not be distended by inflation. There was no nodularity. The impression was malignant lymphoma of the proximal stomach.

Gastroscopey was repeated 19 November. On preliminary drainage, bloody fluid was obtained. At this time the gastroscope was passed easily to depth I. The pylorus, antrum and distal pars media appeared normal and could be inflated well. The proximal half of the pars media showed diffuse intramural infiltration without nodularity. Neither the fundus nor the proximal pars media could be distended. There were no rugae in the region. The mucosa appeared unusually smooth and translucent, but lacked the thinness of atrophy. No vascular channels were visible. Although there was a small amount of blood in the mucous lake, no bleeding source was found. The impression again was malignant lymphoma.

A gastrointestinal X-ray series 22 November by Lt. Col. R. F. Bunch showed delay of entry of barium into the stomach. The body of the stomach was fixed and narrowed, and the mucosa appeared eroded. An infiltrating lesion extended along the lesser curvature from the esophageal orifice, with posterior extension to the greater curvature.

A left supraclavicular node was removed 30 November. The sections showed replacement of the node by sheets and nests of closely-packed oval neoplastic cells with granular eosinophilic cytoplasm. The nuclei were large and ovoid with prominent nucleoli and frequent mitoses. Frequently the cells were composed of coarse reticular networks with peripheral compressed nuclei. In other areas the cells were clumped in cytolytic sheets. There was a marked stromal reaction with dense fibrous trabeculae. Masson stains suggested myoblastic origin. The histopathologic diagnosis was leiomyosarcoma with characteristics compatible with Foote's highly anaplastic leiomyosarcoma of the stomach.

Between 27 November and 19 December the patient received 2700 roentgens (skin dose) X-irradiation each to anterior and posterior gastric portals (1000 KV, total filtration 3 W hlv, 3.6 mm. Pb; 3 ma, 15x15 cm. beam size, distance 70 cm. alt, 85 rpm.).

A third gastroscopey was done 10 December. On pre-

liminary drainage the Ewald tube met an obstruction at 45 cm., but the gastroscope was passed without difficulty. A shelf of tumor, estimated to be 1 cm. in thickness, protruded from the posterior wall about 4 cm. below the cardia. Six smooth, regular, closely-spaced nodules arose from the infiltrated proximal half of the posterior pars media. The mucosa over the nodules was eroded but did not appear to be involved in the tumor process. Again the unusual translucency of the mucosa was noted and was described as resembling pale blood-agar. A single narrow ruga passed by one nodule without distortion. The antrum and pylorus were normal anatomically and functionally.

The patient's course was downhill, and X-ray treatment did not affect its progress. No tumor mass was ever felt. On 8 January 1947 the patient expired.

When the stomach was opened at autopsy (Fig. 1) a flat rubbery submucosal tumor was found to involve the lesser curvature, extending 2 cm. laterally into the anterior and posterior walls. Although the mucosa appeared normal except over the tumor, the gastric wall proximal to the antrum was one-half cm. thick. There was no ulceration or erosion. A 2x2 cm. hemispheric submucosal nodule arose from the posterior wall 2 cm. below the cardia. Microscopic examination confirmed the biopsy diagnosis of leiomyosarcoma.

CASE II

This 21 year old white male was admitted on 16 November 1946 because of anorexia and weight loss of two months' duration. Examination revealed a hard mass filling the left epigastrium. Stools were negative for blood, and there was no free gastric acid.

On 19 November the patient was gastroscoped. The angulus, antrum and pylorus were normal, as was the rugal pattern of the distal half of the stomach. The interior configuration of the proximal half was markedly altered, and it was not possible to distend the lumen by inflation. The reason for this could not be determined, but was thought to be due to intramural infiltration rather than to external pressure. The proximal half of the infiltrated anterior wall was occupied by three uniform 2x2 cm. hemispheric nodules which were soft and smooth;

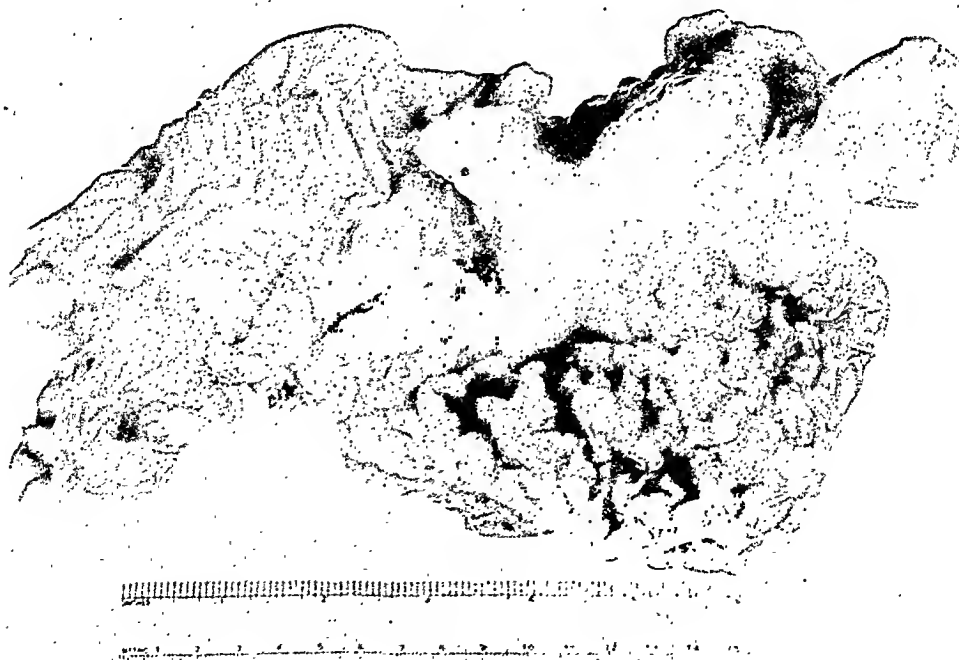


Figure 1 — Autopsy specimen, Case 1.

these were intramural and did not involve the mucosa. There were no rugae in the region. The mucosa everywhere was intact without erosion, free bleeding or gastritic change, but was abnormal in that it showed increased translucency and a bright dark orange color. Highlights were abundant. No vessels were seen. The gastroscopic impression was leiomyosarcoma of the proximal stomach, with lymphosarcoma the important differential possibility.

Gastroscopy was repeated 21 November. The interior configuration of the stomach was again found to be distorted. The infiltrating tumor involved the anterior wall with some extension over the lesser curvature of the pars media to the posterior wall. The proximal half of the anterior wall of the pars media with its three hemispheric submucosal nodules could be depressed by external pressure on the epigastric tumor mass. The smooth soft nodules were again seen to be intramural and free of rugae, and each was estimated to be 2 cm. in diameter. The mucosa was an intense red-orange, and the translucency and increased highlights were notable. The antrum was normal anatomically and could be inflated well. No peristalsis, however, was seen. The impression was leiomyosarcoma.

X-ray studies by Lt. Col. Bunch later the same day showed the distal 6 cm. of the esophagus to be narrowed by extrinsic pressure. There was a mass 6 cm. in diameter in the angle of the cardia. There was another filling defect on the lesser curvature of the antrum, having the appearance of a pedunculated intramural tumor. The roentgenologic impression was twin intramural extramucosal tumors.

On 2 December a laparotomy was done. A large nodular tumor was found extending from the cardia along the lesser curvature and anterior wall almost to the antrum. A biopsy was taken, and histologic examination revealed broad sheets of closely-packed neoplastic spindle cells with abundant fibrillar eosinophilic cytoplasm. The nuclei were hyperchromic and oval to cigar-shaped, with frequent mitoses. The nuclei showed peculiar irregular clumping of the chromatin, producing an atypical vesicular appearance. There were occasional neoplastic giant cells and bizarre ovoid deeply-staining cells. The diagnosis was leiomyosarcoma.

The patient received 23 irradiation treatments between 18 December and 14 January, with 3,000 r skin dose each to anterior and posterior stomach (physical factors as enumerated in Case 1). The mass shrank rapidly, and by 1 January no tumor could be palpated. Nevertheless, the patient continued to lose ground.

At the third gastroscopy 31 December the distal portion of the stomach was normal and the mucosa intact. There was no evidence of the antral tumor noted roentgenologically. The sense of infiltration had disappeared from the posterior wall and now involved only the anterior wall and lesser curvature of the proximal pars media. The three nodules had not changed in configuration but now seemed only half as large as previously. The mucosa over the nodules was eroded and bleeding. The proximal stomach could be distended more widely now. Peristalsis was seen for the first time but was shallow and sluggish.

A repeat X-ray study 10 January showed marked decrease in the size of the antral mass, and the antral mucosa appeared normal. The lesser curvature at the cardia was fixed but no mass was found in the proximal stomach.

Gastroscopy was normal 18 January. The entire stomach could be inflated well and its configuration was normal. There was no evidence of infiltration, tumor or extrinsic pressure. The mucosa and its rugal pattern were normal, with no more than the usual translucency. Peristalsis through the distal stomach was unimpeded and the pylorus responded well.

The epigastric mass again became palpable about 1 February, and two weeks later it was the size of a tangerine. By March ascites began to develop.

The fifth gastroscopy was done 25 March. Drainage brought up several hundred ml. of foul bloody material. There was distortion of the interior stomach, with rigidity of the posterior wall and lesser curvature, and failure of the proximal portion to distend. The posterior wall remained close to the objective and could not be visualized. The anterior wall contained several nodular lesions; the largest, estimated to be 2x2 cm., occupied the anterior extremity of the angulus. Other hemispheric nodules were scattered along the anterior wall. Rugae were absent from the tumor area. The cardia was distorted by tumor, and in this region the mucosa was eroded. The mucosa in the tumorous areas had reverted to the peculiarly bright translucent appearance.

The patient died 27 March, and at autopsy an infiltrating submucosal tumor plaque was found in the anterior wall. The mucosa was not involved. There was a shallow erosion 3 cm. below the cardia. The posterior wall at the lesser curvature was attached to the pancreas with infiltration into that organ. Histologic study showed leiomyosarcoma of the stomach with radiation changes.

COMMENT

The gastroscopic picture described by Schindler and co-workers (1) may be distinctive enough to encourage the gastroscopist to diagnose leiomyosarcoma under certain circumstances. Barowsky's (2) statement that the gastroscopist "... will do well if he is able to establish the malignant nature of the lesion (gastric sarcoma)" may not apply in the case of leiomyosarcoma. The present study, as opposed to Schindler's, indicates that diffuse obviously malignant submucosal infiltration may be seen at times. Then lymphosarcoma may become a difficult differential problem—a problem so important in determining the treatment of choice. Lymphosarcoma may be gratifyingly responsive to roentgen therapy and leiomyosarcoma to surgery, but to be realistic it must be admitted that the radiologist will usually demand a knowledge of the histologic picture prior to treatment, so that the abdomen will probably be opened in any case. This, of course, does not detract from the importance of the gastroscopic method in establishing an accurate preoperative diagnosis.

- Schindler et al (1) emphasized the "softness" and gradually sloping circumference of the nodules as particularly suggestive of sarcoma in their cases. The hemispheric configuration of the protrusions and the succulent appearance of the overlying mucosa were considered significant in differential appraisal of individual cases. In the present study these characteristics forced the gastroscopist to diagnose leiomyosarcoma in one case, in spite of the timidity engendered by such a rare disease. The observed degree of intramural infiltration was not felt to preclude leiomyosarcoma. In the other case the submucosal infiltration was a more prominent feature gastroscopically than the nodules, and, in fact, appeared earlier. No necrotic ulceration was found, although this might well have developed had radiation been withheld.

The outstanding mucosal abnormality was a striking translucency over the tumorous regions. One felt

that he could peer down through a few millimeters of succulent mucosa. The appearance was not that of thinning or atrophy, and no vascular channels were seen. This feature is thought to form a characteristic part of the gastroscopic picture because it disappeared temporarily with other evidences of tumor under roentgen influence, only to reappear with the subsequent growth of nodules (Case 2). It was observed over infiltrating and other nodular tumor growth. The comparison of the appearance with that of blood-agar was used several times in describing the mucosa, and this gives a good approximation of the picture.

The rugal pattern played no part in assisting identification of the nodules. Except at one examination, rugae were absent in the nodular regions, apparently because of submucosal infiltration.

During the early part of the roentgen therapy course, the nodule formation progressed in Case 1. Superficial mucosal lesions appeared in both cases; these were not the changes of post-irradiation gastritis (3). In Case 2 gastroscopy during therapy showed regression of the tumor, a response found also by physical and X-ray examinations. Four days after the completion of supervoltage therapy an anatomically normal stomach with normal peristaltic activity was found. Tumor had disappeared, as had mucosal abnormalities. Nine weeks later all the previously observed evidences of tumor had returned.

Gastroscopic experience with leiomyosarcoma is too limited to permit establishment of precise diagnostic criteria. The importance of the submucosal position of the tumor, of course, is evident. If nodularity is not seen, differentiation from lymphosarcoma, infiltrating carcinoma, and even chronic hypertrophic gastritis often will not be possible. If the picture is that of deep nodularity, benign mesenchymal tumors, true sessile polyposis and, rarely, retroperitoneal tumors (4) may make a differentiation difficult. It is felt that the diagnosis of leiomyosarcoma should be considered if there is intramural infiltration and smooth hemispheric nodules, underlying an unusually translucent mucosa. To be more specific would be to overlook the vicissitudes of the gastroscopic method and of malignant growths.

CONCLUSIONS

As a result of serial examinations of two patients with leiomyosarcoma of the stomach, it is felt that the gastroscopic picture at times may be distinctive enough to warrant inclusion of this tumor among the gastroscopically diagnosable diseases. The present findings were those of malignant intramural infiltration with prominent smooth non-ulcerated hemispheric nodules, and increased translucency of the overlying mucosa. The gastroscopic findings may return to normal temporarily following supervoltage roentgen therapy.

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Diagnostic Techniques in Diarrhoea

By

ALFRED J. CANTOR, M.D.

FLUSHING, N.Y.

THE FIRST STEP in determining the etiology of a particular case of diarrhoea is a complete history. The history will often yield important clues. Furthermore it will recapitulate the treatments that have been utilized to date. Unnecessary repetition of treatment will thus be avoided.

It must be remembered that many cases of diarrhoea are of *psychogenic* origin. A careful history will often point further study in the proper direction.

The *occupation* of the patient should not be overlooked. It may be the source of his diarrhoea. Some cases of metal poisoning will produce diarrhoea. Such metals as mercury, arsenic, lead, gold, bismuth, cadmium and selenium may be the source of diarrhoea. The patient's occupation may point to exposure to various other chemicals or to excessive radiation.

The patient's *habits* should be considered. Excessive smoking of tobacco or excessive alcohol intake may be a source of colon hyper-activity. The dietary habits of the patient should be considered. Diarrhoea may be the result of a dietary deficiency, and may be part of the clinical picture of scurvy, pellagra, beriberi, celiac disease or sprue.

The patient's *past history* should include a discussion of previous operations. Some cases of colon hypermotility are due to adhesions or to anatomical dislocations of the colon produced at the time of surgery on adjacent regions. A consideration of the patient's habits with regard to cathartics and enemas may lead to important conclusions.

The past history should include all questions with regard to *food sensitivity* or *drug sensitivity*. A possible *allergic background* should be considered and questions should include an early history of eczema, hives, hayfever and asthma. The family history should be searched for similar evidences.

The *family history* should include questions with regard to tuberculosis and malignancy.

It is best to have a definite form to follow in all such cases. A form such as the following may be employed:

Name: Age: Occupation:

Address: Telephone: Referred by:

Date:

S.M.D.W. No. of Children:

Present illness:

Number and Character of Stools:

Symptoms: Bleeding; Pain; Cramps; Tenesmus; Incontinence.

Frequency of Attacks and Dates

Pain: Protrusion; Discharge; Pruritus; Abdominal Distress; Laxatives used; Periods of Constipation; Character of the Stool; Weight loss.

Gastro-intestinal Symptoms: Nausea; Vomiting; Heartburn; Appetite; Pain; Hematemesis; Belching.

Habits: Regularity; Coffee; Tea; Alcohol; Tobacco; Sleep.

Past History: Medical; Surgical.

Family History: Tuberculosis; Carcinoma; Miscellaneous.

Psychosomatic Factors: Social background; Emotional life; Personal problems; Sex life; Marital adjustment; Is the disability out of proportion to the disease?

This may seem like a very extensive history form to follow. However, we could also add symptoms referable to the genito-urinary tract, the respiratory tract, cardiovascular system, the nervous system, and the menstrual history. A history form cannot possibly be too complete. It is very essential that all factors be considered in puzzling cases of diarrhoea.

Where there is a direct history of contact and a very typical clinical picture, there is no need to go into an extensive history. If the diagnosis is clinically obvious it is unnecessary to follow through with a genito-urinary and cardio-vascular history. There are many cases, however, in which the diagnosis is not at all evident even after careful exhaustive study. In such cases the history will often point further study in the proper direction.

It is very important that the physician be not brusque in taking the history. The patient must be approached as a human being. He must be considered with sympathy and understanding.

The next diagnostic step is a *complete examination*. A complete physical examination should bear in mind the possibility that the diarrhoea may be of glandular origin. The thyroid should be carefully examined. A fundamental blood dyscrasia may be the source of diarrhoea. Evidences of pernicious anemia, purpura and chronic leukemia should be sought.

The diarrhoea may be caused by disease of the cardio-vascular system.

The upper gastro-intestinal tract may be at fault and require study. The diarrhoea may be gastrogenous or hepatic in origin.

Diarrhoea of acute infectious disease is frequent. This must not be overlooked, especially in children.

We need not here detail any form for the complete general physical examination. I wish to stress merely that it should be as complete as possible under the circumstances. Much information of value to the patient, (both related and unrelated to the diarrhoea), will be uncovered by such an examination.

Nor will I recount the essentials of a proper *anal, rectal and sigmoid* diagnostic study. These details of inspection, digital and instrumental examinations will be found in "Ambulatory Proctology" (1). However, further details of bacteriologic study in diarrhoea cases should be discussed.

The apparatus required for *bacteriologic study* includes:

1. The sigmoidoscope.
2. A warm stage microscope.
3. Slides and cover slips.
4. A sigmoidoscope aspirator (or catheter and syringe).
5. Warm sterile saline solution, culture tubes, culture plates.
6. Needle and tube for agglutination tests.
7. Needle and tube for Wassermann.

Specimens are taken from an ulcerated area. If no gross ulcerations are seen the specimen should be taken from an area of extensive inflammation. The sigmoidoscope aspirator furnishes an ideal instrument for this purpose, as the specimen is removed through the sigmoidoscope under direct vision. Freshly obtained exudate is suspended in saline on a slide and examined on a warm stage. The entamoeba can be readily identified by its motility and clear pseudopodia, and the ingested red blood corpuscles. Cysts may be recognized by their highly refractile, large, chromatoid bodies. The character of the inflammatory exudate is identified at the time of this examination.

In the *Shigella* type of dysentery numerous red blood cells and large macrophage cells will be seen. These macrophage cells may contain red blood cells and pus cells.

Of course the exudate is searched for ova and parasites.

Plates should be inoculated with the aspirated material. These cultures may be made on blood agar, bile salt agar, and eosin methylene blue. Culture may also be taken in glucose broth.

Smears may be made and studied with acid-fast stains, gram stain, and Heidenhain's iron-hematoxylin stains.

In some cases it might be desirable to use SS agar or desoxycholate agar. If it is desired to study for bacteriophage plain broth tubes may be inoculated.

It is necessary to do repeated studies if the initial studies are negative. These studies should be repeated daily or on alternate days. If they continue negative after five to seven such studies the diarrhoea may be considered of non-bacterial origin.

If a recto-sigmoid aspirator is not available, material for culture may be obtained by a sterile catheter. This catheter is inserted into the rectum and material is aspirated with a sterile syringe containing five cc. of sterile saline. Place the aspirated material in a sterile test tube and send to the bacteriologist.

A blood specimen may be required for dysentery and salmonella agglutination tests. Ten cc. of blood will be required for these studies. A complete blood count is also indicated in most cases. The sedimentation rate should be determined in all chronic cases. If indicated the blood should be studied for malaria parasites. In occasional cases a coagulation and bleeding time will be required. A blood chemistry is often desirable. This chemistry should include a study of serum phosphorus and calcium, as well as determinations of urea nitrogen, sugar, cholesterol and chlorides. In some cases the serum protein should be determined, and particularly the albumen-globulin ratio. In other cases it may be desirable to determine the prothrombin time of the blood. Occasionally the ascorbic acid content of the blood should be estimated.

A *Wassermann test* is routine in all cases. The *complement fixation test of Craig* is of value in cases of suspected amebic dysentery.

A *urinalysis* should be performed in all cases of chronic diarrhoea. A microscopic urine examination will be useful in controlling sulfonamide therapy by providing early findings of acetyl sulfonamide crystals and red blood cells in the centrifuged urine sediment.

Analysis of aspirated *gastric contents* is of value in many cases of diarrhoea. Diarrhoea may be caused by achylia or achlorhydria. Aspiration of *duodenal contents* is of particular value in the search for *Giardia lamblia*.

A *basal metabolic rate* determination is valuable in many cases of diarrhoea. Interpretation of the result must be cautious, however, inasmuch as a severe anemia or a high fever may produce a high basal metabolic rate. Taken in conjunction with other findings a diarrhoea of hyperthyroid origin may thus be diagnosed.

Skin tests are of value in cases suspected of an allergic background. A routine Frei test is indicated, and should be repeated when there is any suspicion of lymphogranuloma venereum.

Roentgen studies are routinely performed in all cases of chronic diarrhoea. Barium may be given by mouth to determine the function of the colon. The barium

enema is given to determine the physical structure of the colon. In many cases a complete gastro-intestinal study is indicated, including a study of the esophagus, the stomach, the duodenum and the remainder of the small intestine, as well as the colon.

All barium enema studies should include an air-contrast film. The detailed technique of these studies need not be given here. Unless the proctologist is particularly adept in the use of the fluoroscope and in the interpretation of roentgen films, he would do best to refer the patient to the roentgenologist for such study.

Biopsy may be necessary for diagnosis in certain cases of chronic diarrhoea. A specimen taken from the margin of an ulcer, or scrapings from an ulcer site, may reveal the presence of the *Entamoeba histolytica* in cases of amebic dysentery. The complicating

polyps of ulcerative colitis must always be biopsied.

A *therapeutic test* may be required for diagnosis in cases of suspected amebiasis. This should be done only after repeatedly negative studies for the *Entamoeba histolytica*. If such studies are repeatedly negative in a case clinically suggestive of amebiasis, a therapeutic test may be performed by the administration of anti-amebic drugs, with a study of the therapeutic response.

Test diets are of value when a diarrhoea of probable allergic origin is presented. The suspected allergen is eliminated from the diet. The most common allergens are wheat, milk, cabbage, eggs, tomatoes, oranges and chocolate.

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Observations on Acute Allergic Gastritis

By

THEODORE C. AFENDOULIS, M.D.

ATHENS, GREECE.

THE GASTRO-INTESTINAL SYSTEM plays a prominent role in the manifestation of allergic diseases. It not only permits the absorption of antigens but also presents clinical manifestations and anatomical changes of an allergic nature. From the point of view of the stomach especially, there are certain disorders which constitute a group of special clinical symptoms under the name of "gastropathia allergica" — a term which means that a process takes place, which is not inflammatory in origin.

Pain of varying intensity and duration, usually in the epigastrium, acid regurgitations and a feeling of burning in the stomach or esophagus are the usual symptoms of allergic gastropathy. These are followed practically always by the classical manifestations of allergy, i. e. urticaria, pains at the joints, etc.

Rowe found, by examination of the gastric acidity, normal values both of free acid and total acidity in 80% of his cases. On the other hand Gay found anacidity, while Chevallier reports normal values in 50% of his cases and hyperacidity in 25% or hypoacidity in the remaining 25% of his cases.

Rowe and Wiedemann after X-ray examination found pylorospasm, increased peristaltis and delayed emptying of the stomach. These findings were attributed to a general or localised edema of the mucous membrane together with spastic contraction.

From the Department of Clinical Medicine of Evangelismos Hospital, University of Athens.

Submitted September 25, 1947.

R. Chevallier reports cases with incomplete filling of the pyloric antrum due to a swelling of the walls of the stomach, and with defects of the lesser and greater curvature identical with those seen in gastric cancer, except that these defects were not permanent.

Kaijser (1937) was the first to propose the substitution of the term of "allergic gastritis" for that of "allergic gastropathy." He based his proposal on the histological findings of the stomach of a patient presenting allergic sensitiveness towards onions, and who was gastrectomized owing to suspicion of gastric ulcer.

Hansen and Simonsen (1938) reported a case of a patient with sensitiveness towards egg albumin manifested by gastric disorders, pain, vomiting, urticaria and angioneurotic edema. Radioscopy of the stomach was negative between attacks. On the contrary after supplying egg albumin, in the resulting allergic attack, pylorospasm, swelling and serpent-like appearance of gastric folds were found. Hansen and Simonsen considered the above reaction of the stomach as inflammatory in nature and included it in the group of "allergic gastritis" described by Kaijser.

Knepper (1936) and Kaiserling and Ochse (1938) following the research work of Rössle and Klinge on local allergic hyperergic inflammation, produced allergic changes of inflammatory origin on stomachs of rabbits and guinea pigs.

In 1938 in collaboration with Gülzow, we reported the results of our experiments made on dogs in the

laboratory of Prof. Katsch in Greifswald, Germany.

After repeated gastroscopies, examinations of the gastric acidity and histological study of the mucous membrane of the stomach, we found that in dogs sensitized to horse serum, an acute gastritis with hyperacidity is caused after intravenous reinjection of the same antigen. Thereafter in 1943, we reported our first case of acute allergic gastritis diagnosed gastroscopically on a patient with allergic sensitiveness towards quinine and manifested by acute illness and urticaria appearing immediately after administration of quinine by mouth.

CASE REPORTS

Case 1: G. T., age 42, female. Scarlet fever and whooping cough in childhood. Malaria at 25 years, cured. Menstruation normal. For the past 15 years complains of pains in the joints especially in winter, and for the last twelve months of arthralgia, with permanent involvement of the knees and the small joints of the feet with atrophy of the legs. Further physical examination showed nothing abnormal. Tonsils normal. A full mouth roentgen-ray was not performed owing to the war and the enemy occupation conditions. Sedimentation rate increased. Other laboratory tests normal. Treatment: Salicylate, sulfanilamide, progynon, gold therapy. On 25/7/42 we granted the patient 0.25 antipyrine by mouth. Half an hour later the patient showed a severe reaction consisting of sudden exacerbation of the symptoms of arthralgia, followed by nausea, vomiting, epigastric distress and urticaria. The next day the same dosage of antipyrine provoked again the above mentioned allergic local and general manifestations. Four days after the second attack, we proceeded to a detailed examination of the patient's stomach. Gastroscopy, X-ray and the gastric acidity, normal. Maximum values of acidity: Free acid, 36. Total acidity, 56. The same tests during allergic attack after the administration of 0.25 gr. of antipyrine twice in a week gave the following results: Free acid, 58. Total acidity, 90. The relative difference in the values of free acid and total acidity is due to the presence of blood in the gastric juice. Gastroscopy: The gastric folds of the body of the stomach and especially the anterior wall, swollen and edematous in certain parts. Mucous membrane swollen, of dusky red color with much graywhite mucus between the folds.

These changes are increased in the area between the body and the pyloric section with localized hemorrhagic lesions of the mucous and the submucous membrane. Spasm of the pyloric section was noted. Diagnosis: Acute allergic hemorrhagic gastritis with hyperacidity.

Case 2: Add. A., age 43, male, farmer. A year ago malaria for two weeks, treated and cured by quinine. Six months ago after eating curdled milk, reports epigastric distress, followed by vomiting, acid regurgitations and urticaria. For the last ten days patient complains of malaria fever of tertian character, untreated. Two days before admission in the hospital and after eating curdled milk, patient had a sudden feeling of burning all over his body, followed by urticaria, hyperemesis and epigastric distress. On physical examination we found urticaria especially on the chest and abdomen. Spleen enlarged. Laboratory tests: Normal. In thick blood-films subtertian rings and crescent forms of the plasmodium

of Laveran. Gastric acidity: (maximum values). Free acid, 10. Total acidity, 28. X-ray: Nothing important. Gastroscopy: Mucous membrane of the body of the stomach and pyloric section pale, of light red-gray color. Folds thin, elastic. At the posterior wall of the body and the lesser curvature, mucous membrane swollen and red. Intense light reflexes all over the stomach due to the presence of abundant transparent mucus. Diagnosis: Subacute allergic gastritis on the ground of chronic gastric atrophy with hypo-acidity.

Case 3: Ir. E., age 25, female. At eight years of age epidemic cerebrospinal meningitis, cured by serotherapy. At 11 years typhoid fever. Menstruation normal. Patient reports epigastric distress, nausea and vomiting which started a few hours before admission in the hospital after eating cheese. By physical examination, sensitiveness in the epigastrium and abdomen. Urticaria noted, especially on the chest. Laboratory tests: normal. Gastric acidity: Free acid, 48. Total acidity, 74. X-ray: Nothing important. Gastroscopy: Mucous membrane of the stomach and especially the anterior wall near the lesser curvature, swollen and flushed. In the pyloric section those changes are more increased with dusky red coloration of the mucous membrane and two small erosions. Abundance of mucus did not allow minute examination. Diagnosis: Acute allergic gastritis, especially of the pyloric section, with hyperacidity.

DISCUSSION

We consider the above cases interesting owing to the fact that by gastroscopy and the examination of the gastric acidity we found changes suggesting a process of inflammatory origin. The changes of the gastric mucous membrane are like those found in the common, non-allergic, acute gastritis according to researches on the latter form especially by Henning. The only difference is that in allergic gastritis the reaction of the stomach is of an hyperergic nature, i. e. although characterized by the same signs as the common gastritis, it differs from the latter in its intensity and the suddenness of onset.

The almost immediate manifestation of the symptoms as soon as the antigen contacts the gastric mucous membrane and the enormous intensity of the inflammatory processes constitute the special characteristics of the acute allergic gastritis. We think that this form of gastritis is to be classified within the endogenous gastritis group of Faber and Kaufmann. It is due, as already known, to products of incomplete breakdown of proteins and mainly to histamine or histamine-like substances, acting directly on the gastric mucous membrane. Repeated appearances of attacks of allergic gastritis may lead to chronic gastric atrophy with anacidity. This may be, we think, a good explanation of the cases of atrophy of the gastric mucous membrane described by Gutzeit and Teitge, H. and F. Voss and Moutier and Chevallier in some cases of allergic diseases, especially of the skin. Further research work on allergic gastritis is necessary.

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Increased Sugar Tolerance as a Factor in the Production of a Symptom Complex Simulating Peptic Ulcer, Neuro-Circulatory Asthenia, and Psychoneurosis

By

A. ROBERT PESKIN, M.D.

NEW YORK, N. Y.

THE MIMICRY OF DISEASE has always been a great factor which is responsible for embarrassment to the physician and the plaguing of the patient. The exact explanation for the occurrence of a group of symptoms is the job of every physician. This requires often a keen understanding of physiologic principles and bio-chemical changes. The artful side of medicine is the interpretation of such symptoms and their relationship to an underlying pathologic state.

This bizarre symptom complex is characterized by post-prandial abdominal pain and is brought on by physical effort and hunger. Food provides instant relief and rest is apt to lighten the symptoms. Off-hand, such a picture suggests peptic ulcer. However, the problem is made more baffling and complex by persistently negative roentgenological findings in repeated gastro-intestinal studies. Usually these conflicting observations result in the internist's dissatisfaction with and skepticism of the roentgenologic report.

When a further and detailed check of the patient's history is attempted, such symptoms as palpitation, air-hunger, apprehension, excessive sweating, weakness in the legs and marked tremors are encountered. If these attacks are not ameliorated by rest or the intake of food, mental confusion and light-headedness frequently follow. When no stress is laid on the post-prandial character of the abdominal pain often occurring with the above group of symptoms, the symptom complex is frequently labeled neurocirculatory asthenia. However, the cardiologist rarely finds any abnormality in the heart. Physical examination, roentgen-ray, or electro-cardiographic study contribute

little to the diagnosis of neuro-circulatory asthenia. At this point the problem is usually considered neuro-psychiatric. The psychiatrist, assured that no organic disease has been found, decides that the patient falls into the category of neuro-psychiatric diseases and recommends psychoanalysis, etc.

In approaching this perplexing problem, a study was made of a group of cases in which, despite the presence of the ulcer syndrome and nervous symptoms, X-ray findings were negative. Recalling the similarity of symptoms produced by a drop in blood sugar to the post-prandial pain in ulcer patients, and the regularity with which the pain occurs in both of these circumstances, a study of the fasting blood sugar in these cases revealed a very slight and not convincing drop in the blood sugar during the pain interval. Since this finding might well be a coincidence, more reliable and irrefutable evidence was sought in establishing the relationship between the slight drop in blood sugar and the occurrence of abdominal pain. A study of the sugar tolerance resulted in a very striking and dramatic disclosure. Not only was the fasting blood sugar at the lower limits of normal, but administration of sugar by mouth lowered the blood sugar even further. In some instances the blood sugar curve, after administration of the standard 100 grams of glucose, was a mirror image of the normal blood sugar curve under identical conditions. In other words, here were instances of paradoxical responses to sugar ingestion — a condition which is the direct antithesis to diabetes mellitus. It was obvious, therefore, that these were patients with a metabolic disturbance, in whom hunger contraction and pain were precipitated by a drop in the blood sugar level below a certain threshold specific for the particular individual. That these instances were not isolated and rare was shown

by me in 1937 in a study of a group of such cases picked at random in a large gastro-intestinal clinic. To demonstrate this syndrome, the following cases are presented:

CASE I

HISTORY: A 20 year old male, white, well-built and well nourished, not appearing acutely or chronically ill, presents himself with the following complaints:

- C. C. 1. Pain in abdomen coming on when he is hungry or after severe physical effort and relieved by eating particularly sweets.
2. Nervousness and trembling.
3. Dizziness.
4. Perspiration.
5. Light-headedness.
6. Lassitude and extreme fatigue.
7. Air hunger.

PRESENT ILLNESS: The patient was well up to four years ago. At that time he began to experience the above train of symptoms. It was also about that time that he began to work. His most unpleasant sensation was a burning pain or discomfort in the abdomen occurring when hungry. This would be relieved by eating, particularly sugar and water. If food was not available, pain would greatly increase in intensity, and with it the patient would experience a trembling and shaking all over, nervousness, confusion, inability to catch his breath, profuse perspiration, and dizziness. He also noted that these symptoms were more apt to come on when he was working or carrying on other physical exertion. During periods of relaxation or freedom from physical effort, or while at rest in bed, he would not be prone to get these attacks. The type of food eaten would make no difference as to onset of attack if he were resting. However, under conditions of physical exertion spicy and rough food would be intolerable. This train of symptoms continued up to the present day almost without a significant remission. In fact on induction into the army his symptoms became aggravated. On extended drills or hikes he would be forced to fall out because these symptoms would come on with great intensity and rapidly. Since admission to the hospital, even on a standard ward diet, the patient has had no symptoms.

FAMILY HISTORY: Patient's father had similar symptoms and discovered that he would get instantaneous relief from ingestion of sugar and water. Father's sister suffered a similar condition. There were no other relevant family illnesses.

PAST HISTORY: Outside of the ordinary childhood diseases the past history was non-contributory.

ASSOCIATED TRACTS:

Gastro-intestinal: Pain in abdomen 2 - 3 hours after eating, brought on sooner during work or other exertion and relieved by rest and food — particularly sweets. Belching and sour eructation are also sometimes present. Pain is relieved by alkalies, aggravated by fats and rough food.

Cardiac: Dyspnoea during attack of pain and exertion relieved by rest and food. No edema, no palpitation, no precordial pain.

Respiratory: Negative — except for air hunger or "As-thina," as patient explains during such attacks of pain, no cough.

Neurological: Trembling all over, nervousness, headache, apprehension, sweating, light-headedness, dizziness, mental confusion and extreme lassitude and fatigue coming on with attacks of abdominal pain, particularly brought on by physical effort and relieved by food.

LABORATORY:

Urine:
Color Straw Reaction Acid
Sp. Gr. 1.016 Microscopic Negative
Character Turbid
Albumin 0
Sugar 0
Sugar Tolerance:

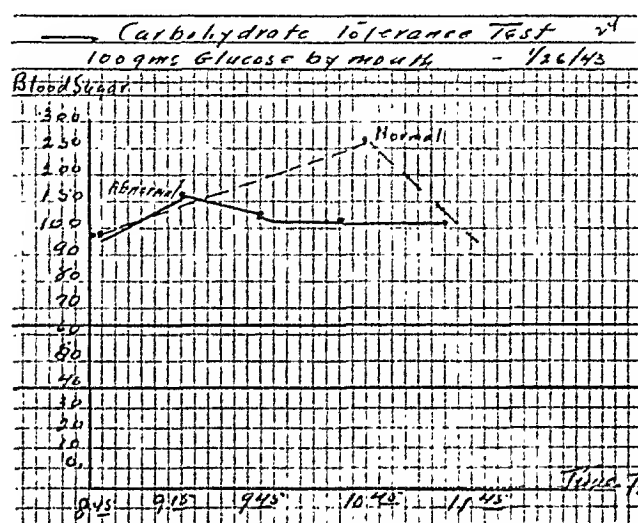


Figure 1

January 26, 1943

8:45 - 97.6 mgm.%
9:15 - 159 mgm.%
9:45 - 127 mgm.%
10:45 - 118 mgm.%
11:45 - 105 mgm.%

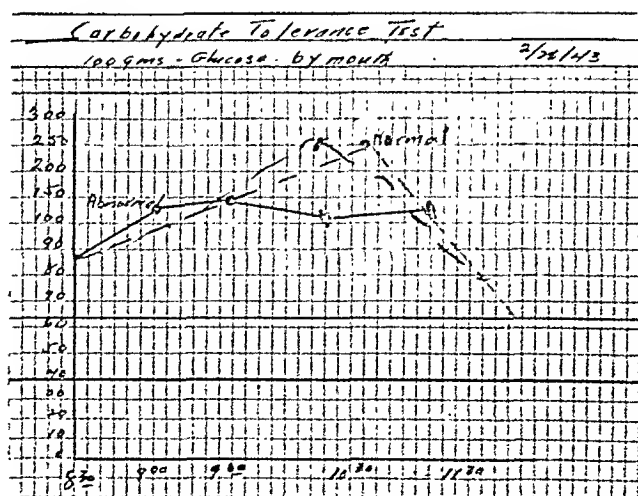


Figure 2

February 2, 1943

8:30 - 91.5 mgm.%
9:00 - 127 mgm.%
9:30 - 109 mgm.%
10:30 - 91.5 mgm.%

Carbohydrate Tolerance Test

100 gms. Glucose by mouth - 2/2/43.

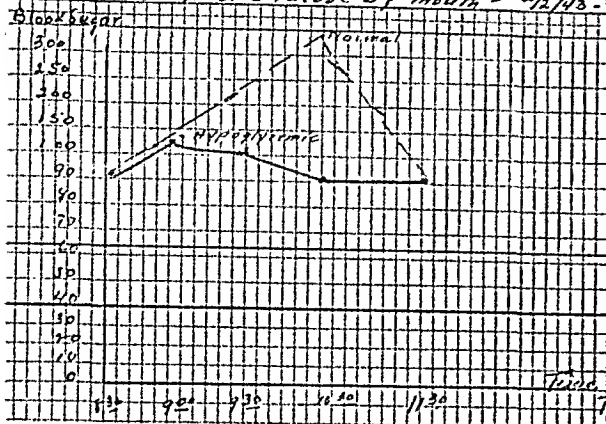


Figure 3

February 26, 1943

8:30 - 88.1 mgm.%
 9:00 - 132.4 mgm.%
 9:30 - 148 mgm.%
 10:30 - 119 mgm.%
 11:30 - 134 mgm.%

X-Ray EXAMINATION:

G. I. — 1-30-43. No evidence of gastric or duodenal pathology.

Skull: 2-6-43. Sella Turcica is of average depth. The clinoid processes do not appear eroded.

LIVER FUNCTION TESTS:

1. Galactose Tolerance — Administration of 40 gms. of galactose in 250 cc. water and the urine collected for five hours. The determination of the amount of galactose excreted in five hours disclosed less than 3 gms. excretion, which shows good liver function.

2. Hippuric Acid Test — This test measures the ability of the liver to synthesize hippuric acid from benzoic acid. Six gms. of sodium benzoate, as recommended by Quick, is given by mouth. The urine is then collected for four hours. From this urine the hippuric acid content is determined quantitatively by one of several ways. A diminished output of less than 1.5 gms. is interpreted as an inability on the part of the liver to convert benzoic into hippuric acid. The inability to synthesize hippuric acid is suggestive of liver dysfunction.

HIPPURIC ACID TEST

Specimen	Volume	Hippuric Acid Amt.
1.	48 cc.	0.00
2.	62 cc.	.29 gms.
3.	63 cc.	.46 gms.
4.	76 cc.	.66 gms.
5.	48 cc.	.51 gms.

Total of 1.92 Hippuric Acid excreted in four hours and converted from Benzoic Acid.

BLOOD CHEMISTRY: 2-8-43.

	Found	Normal
Cholesterol	258.0	160-200
Calcium	11.9	9-11
N. P. N.	37.5	20-35
Phosphorus	3.6	3-4
Chlorides	350.0	400-500

B. M. R.

1-28-43. Minus 24.
 2-9-43. Minus 2.

Serology:

Kahn — Negative.

Blood Count:

R. B. C. — 4,610,000.
 W. B. C. — 9,000.
 Hb. — 85.
 Diff. — Seg. 66; Lymph 34.

Gastric Analysis: 2-13-43.

	Total	Free HCl
8:00 A. M. fasting	52	26
8:30 A. M.	46	34
9:00 A. M.	34	8
9:30 A. M.	28	0

After the 8:00 A. M. specimen, 20 cc. of 95% alcohol in 100 cc. of water was given.

INSULIN TOLERANCE TEST

12 U. Insulin given at 8:30 A. M.

TIME	Blood Sugar	REACTION
8:30 Fasting	102 mgms.	Patient feels well, no symptoms, no weakness, no tremor, no dizziness
Insulin given 9:00 A. M. 1/2 Hr. after Insulin	91.3 mgms.	Patient feels well, no complaints
9:15 — 3/4 Hr. after Insulin	77.8 mgms.	Patient feels weak, breathes heavily, as in air hunger, and has marked tremor. Is hungry and somewhat dizzy. Has weak feeling in stomach.
9:45 — 1 1/4 Hr. after Insulin 2nd dose of 20 U. of Insulin given at 9:45.	100.8 mgms.	Patient feels somewhat better. Above symptoms are less marked.
1 Hr. 45 Min. after 1st dose of insulin 1/2 Hr. after 2nd dose of Insulin 20 U.	88.5 mgms.	Shortness of breath, tremors, nervousness and weak feeling in stomach quite marked.
2 Hrs. 20 Min. after 1st dose of insulin and 1 Hr. after 2nd dose of Insulin	74.1 mgms.	Weakness in legs, nervousness, tremors, sweating, empty feeling in stomach, air hunger and dizziness. After ten minutes of exercise, breathing became deeper, as in air hunger. Patient complained of weakness, palpitation, nervousness, dizziness, suffering was marked. Coarse tremor of hands. BP 110/80. After another 5 minutes of exercise, patient became pale, ashen-gray, the tremor became more marked, things became black before his eyes and he felt faint. A glass of orange juice was given and he felt better in about five minutes.
2 1/2 Hrs. after 1st dose of Insulin in 175 Min. after 2nd dose of Insulin and 15 min. after orange juice.	133.3 mgms.	Patient felt better. All symptoms disappeared. No effects from test.

To a patient who has been on a standard ward diet consisting of protein, carbohydrates, and fats twelve units of insulin was given subcutaneously. This was followed by administration of a second dose of 20 units of insulin, 1 1/4 Hrs. later. Throughout this study, 1/2 hourly determination of blood sugar was done. The development of symptoms resembling hypoglycemia and the time they became evident was recorded. It was our intention to observe at what blood sugar level symptoms first appeared, the progress of these symptoms and their significance to the patient's original complaints. From this study it was concluded that the patient begins to display symptoms of hypoglycemia about 3/4 of an hour after the first dose of insulin is injected. The level of blood sugar at which symptoms appear is 77.8 mgms. %. The symptoms continued until the second dose of insulin, in the amount of twenty units has been given subcutaneously. About one hour after the second dose of insulin the patient's symptoms became markedly exaggerated and aggravated, he developed weakness in his legs, marked nervousness, apprehension, exaggerated tremor of his hands, sweating, empty feeling in his stomach, air hunger and dizziness. After ten minutes of exercise, breathing became deeper, as in air hunger. The patient complained of weakness, palpitation, nervousness, dizziness, and apparently was suffering markedly from these symptoms. His blood pressure was 110/80. After five minutes more of exercise, the patient became pale and ashen-gray in color, the tremor became more marked, he experienced black-out and he felt faint. At this point orange juice was given. In about five minutes the patient began to feel better and gradually all his symptoms disappeared within 15 minutes after the orange juice ingestion. The implications of this test and its results will be dealt with in detail in the discussion.

Three more cases are described and reported here to demonstrate this concept. Unfortunately we had no opportunity to study these cases with the same detail. It is not a fortuitous circumstance that the revelation of an actual or relative hypoglycemia was disclosed in these cases with a bizarre symptom complex simulating peptic ulcer, neuro-circulatory asthenia, or neurasthenia. The administration of insulin precipitated symptoms which were identical with those in the original complaints. The similarity in symptoms in the insulin injected individual before and after the administration of the drug was so striking as to call forth the spontaneous exclamation, "Doctor, this is exactly how I feel when I get these attacks." The significance of these symptoms and the mechanism in their production will be dealt with further in the discussion.

CASE II

- C. C. 1. Pain in pit of stomach.
2. Sweating.
3. Weakness.
4. Giddiness.
5. Trembling and shaking all over.
6. An inner feeling of apprehension.
7. Fainting.
8. Weakness in the knees.
9. Palpitation.

PRESENT ILLNESS: Patient had been well and free of symptoms up to five years ago at which time he began to experience a peculiar gnawing pain in the pit of the abdomen to an area about the size of a silver dollar. This pain was not radiating. As a rule the pain persisted continuously if he hadn't eaten. Occasionally, the patient would be awakened at 4 A. M. from his sleep, and he

would have to eat something or the pain would continue until breakfast time. When he had this pain and took food, he experienced immediate relief. This subsidence or freedom from pain lasted only 1/2 to 1 hour and then returned. If food was not available patient suffered agonizing pain. He observed that any kind of food, even highly spiced, seasoned, or acid foods, provided relief. However, fried foods and fats, particularly fried eggs gave no relief but aggravated his pain. Bicarbonate of Soda gave some relief for about one hour. Fruit juices in particular gave instantaneous but short-lived relief. When for some reason food was withheld, he would become extremely nervous, shake all over, his hands trembled, he sweated profusely, became light-headed and giddy and, if not relieved at this point, he would faint. After period of unconsciousness, he'd feel weak and dizzy. During such periods of food abstinence he also experienced palpitation, shortness of breath, a feeling of air-hunger, and a peculiar sense of apprehension, unrest and jitteriness. All these symptoms would be precipitated or aggravated and very severe when he was engaged in heavy physical effort, or, on long forced hikes. When at rest and relaxed the symptoms were much milder and sometimes non-existent. As a result of this, the patient was forced to stay away from work for a long time. He suffered neither heart-burn, belching, nausea, vomiting nor other gastro-intestinal symptoms. Sippy diets were somewhat helpful, but not completely so.

FAMILY HISTORY: His father, similarly, had been troubled with exactly the same symptoms including vomiting for the past five or six years. He had been told he had ulcer of the stomach. His mother had "stomach trouble" which has been diagnosed as "gall bladder" disease. She has, however, been free of symptoms since an operation 15 years ago. Patient does not know what the operation was for. All siblings are well. No cancer, no diabetes, or any other known disease in the family.

PAST HISTORY: Has been in good health up to the present illness, which began 5 - 6 years ago. Has had measles only and no other infections or illnesses.

ASSOCIATED SYSTEMS:

Gastro-Intestinal: As in present illness.

Cardiac-respiratory: Attacks of palpitation and a peculiar deep breathing and a feeling of air hunger during attacks of abdominal pain.

G. U.: Negative.

SUGAR TOLERANCE CURVE:

First Test	3-4-43	3-17-43	3-24-43
8:05	101	8:25 — 98	8:20 — 103.6
8:35	152	8:55 — 189	8:50 — 160
9:05	106	9:25 — 179	9:20 — 210
10:05	104	10:25 — 104	10:20 — 83
11:05	59	11:25 — 110	11:20 — 66
12:05	59		
1:05	90.5		

G. I. X-ray Studies:

May 4, 1942 — No evidence of organic disease of the stomach or duodenum. Peptic ulcer searched for and ruled out.

March 6, 1943 — No evidence of organic disease of the gastro-intestinal tract. Peptic ulcer of stomach or duodenum not found.

X-ray of Sella Turcica — Normal in all respects.

X-ray of Gall Bladder by means of dye — reveals no evidence of disturbed function or disease of this organ. The gall bladder is visualized, the dye is normally concentrated, and emptying is normal. There is no evidence of calculus formation.

Blood Chemistry: Cholesterol — 237 mgms.

Basal Metabolic: Rate — 17%.

Gastric Analysis:

	Total Ac.	Free HCl
Fasting Specimen	50°	36°
First Specimen	70°	48°
Second Specimen	84°	58°
Third Specimen	86°	60°

Kahn: Negative

Blood Count: Hb — 90%. Smear within normal limits.

Urinalysis — Normal.

CASE III

C. C. 1. Burning across abdomen.

2. Trembling.

3. Nervousness.

4. Weakness.

5. Faintness.

6. Sweating.

PRESENT ILLNESS: For the past 3 - 4 years patient has experienced a peculiar burning sensation in abdomen present only during summer and not during winter and only under conditions of exertion. While food has no definite relation to this pain, he had observed that hunger would accentuate it and also precipitate trembling of the hands, weakness and shaky feeling in the knees, profuse sweating, and faintness. As the patient himself expressed it, if he doesn't eat "he can't keep himself together." A short hike is accomplished without trouble, but on long sustained physleal effort he would suddenly experience darkness before his eyes, nervousness and trembling all over. A cold drink of water, he observed, would ease burning sensation in his abdomen. At times after hard work he would get giddy — as if he were drunk. Patient has observed that he always hated sweets and candy or sugar since childhood.

PAST HISTORY: Had typhoid, pneumonia, measles, chicken pox and whooping cough.

FAMILY HISTORY: Mother died at fifty-four, from a stroke. Father is alive and well. Three sisters and seven brothers alive and well. No diabetes.

ASSOCIATED TRACTS:

G.I.: Except for this burning in abdomen, patient's appetite is good and he has no other symptoms.

Cardiac: Negative.

Respiratory: Negative.

G.U.: Negative.

Physical:

Blood Pressure — 110/80

Heart — Negative.

Lungs — Negative.

Abdomen — Negative.

Laboratory:

Fasting Blood Sugar: 3/19/43 — 61 mg.

3/23/43 — 101 mg.

Urinalysis: Sugar — Negative

Trace — 3/21/43

2 + — 3/23/43

1 + — 3/24/43

CASE IV

CHIEF COMPLAINT: Epigastric pain of five years duration.

PRESENT ILLNESS: Patient is a white male soldier of about twenty-five years of age who was admitted because of constant epigastric distress, which he has had almost constantly for five years. He is of modest habits, drinking occasionally and only moderately, and smoking about ten cigarettes daily. His family history revealed that his father suffered from a similar ailment. With the exception of this present illness, his past history was uneventful.

For five years, this patient has had intensive, sharp epigastric pain relieved by food and alkalies. He has noticed that fatty, greasy, or fried foods would precipitate an attack of pain or aggravate existing pain, otherwise, pain is not related to food intake and does not radiate. The character of the pain is described as "aching." He has no sour eructations and no hematemesis, however, he is nauseous when he has the pain and vomits only occasionally. At the time of admission, the patient stated that he had tarry stools only once, immediately before admission. There were no other relevant facts.

This patient has had four subsequent admissions to this hospital, for identical complaints. He has had no relief from careful ulcer management.

Physical Examination:

Head, eyes, ears, nose, and throat revealed no unusual abnormalities. Heart and lungs were normal.

Abdomen: Disclosed no masses, rigidity, or tenderness, and no scars or palpable enlargement of the liver, spleen, or kidneys.

Laboratory Studies:

Blood Count: RBC —	5,510,000
WBC —	8,900
HC —	94
Differential — Polys —	75
— Lymphs —	25

Urine: Negative.

Wassermann: Negative.

Stool: Negative for blood and parasites.

4/22/43 — Gastric Analysis:

Time	Total Acid	Free Acid
7:45 A. M.	45°	36°
8:45 A. M.	95°	83°
9:15 A. M.	64°	58°
9:45 A. M.	59°	52°
Lactic Acid:	None.	
Blood	None	

6/27/43 — Gastric Analysis:

Time	Total Acid	Free Acid
8:00 A. M.	50°	36°
8:30 A. M.	70°	48°
9:00 A. M.	84°	58°
9:30 A. M.	86°	60°

2/14/43 — Blood Sugar:

Time	Blood Sugar	Urine
8:10 Fasting	91.3	Negative
8:40	146	Negative
9:10	104	Negative
10:10	70.7	Negative
11:10	51.3	Negative

3/17/43 —

Time	Blood Sugar	Urine
8:20 Fasting	103.6	Negative
8:50	160	Negative
9:20	210	Negative
10:25	83	Negative
11:20	63	Negative

3/24/43

Time	Blood Sugar	Urine
8:25 Fasting	98	Negative
8:55	189	Negative
9:25	179	Negative
10:25	104	Negative
11:25	110	Negative

4/1/43

Time	Blood Sugar	Urine
8:05 Fasting	101	Negative
8:35	151	Negative
9:05	106	Negative
10:05	104	Negative
11:05	59	Negative
12:05	59	Negative
1:05	90.5	Negative

6/28/43

Time	Blood Sugar	Urine
8:30 Fasting	85.1	Negative
9:30	131.6	Negative
10:00	112.0	Negative
10:30	115.6	Negative
11:30	82.6	Negative
12:30	63.6	Negative
1:30	160.	Negative
2:30	109.	Negative

ROENTGEN STUDY: 2/25/43 — G. I. Study: Revealed no evidence of ulcer in stomach or duodenum.

4/20/43 — G. I. Study: Revealed no evidence of ulcer in stomach or duodenum.

Gall Bladder Study with Dye: Dye given after supper on March 22, 1943. Films were taken the following day at 9:00, 11:00, 1:00, and 3:00. The gall bladder visualizes well in the first two films, revealing a homogenous shadow. On the third film taken after a fatty meal, the gall bladder appears to be about one-half empty. In the fourth film, the gall bladder seems to be about one-fourth filled. Conclusion is that the gall bladder reveals evidence of sluggish functions.

X-Ray of Skull: Sella Turcica is normal in all respects.

BASAL METABOLIC STUDY:

3/2/43: —17.

3/31/43: —24.

BLOOD CHOLESTEROL:

237 mgms. in 100 cc. of blood.

CONCLUSION: A white male was admitted to the hospital four times for the invariable complaint of epigastric pain, occasionally relieved by food and alkalies, but who on a strict Sippy regime with Belladonna, showed no tendency to a remission. On all these admissions there were no unusual contributory physical abnormalities noted. The X-ray examination of the gastro-intestinal tract showed no evidence of peptic ulcer. Gall Bladder study, however, disclosed slight sluggishness in emptying on the part of the gall bladder.

The only constant and pertinent finding which suggested the underlying cause for his symptoms was a persistent increased sugar tolerance or low sugar tolerance curve on four different occasions. Although the fasting blood sugar was not abnormally low, on any of the examinations, the administration of 100 gms. of sugar by mouth after determining the fasting level, invariably revealed a slow and insufficient rise in the blood sugar level on the first two or three half-hourly interval determinations. Subsequently, the blood sugar dropped to an unusually low level, which could be distinctly considered hypoglycemic. The lowest level reached 50 mgms. Interestingly, following the lowest recording of blood sugar, there was a spontaneous rise of the blood sugar to about the normal fasting level. The interpretation of this, is rather a moot point. Perhaps it is due to an exhaustion of the insulin which was stimulated by the ingestion of the sugar, or perhaps again the abnormally low sugar level in the blood stimulated glycogenesis on the part of the liver. Indeed, there is also the possibility that the abnormally low sugar in the blood stimulated the secretion of adrenalin with the subsequent increase in the blood sugar content.

A repeated basal metabolic determination showed a minus 17 and a minus 24 on two different occasions. This finding again suggests the sluggish state of the thyroid which is commonly observed in this condition.

DISCUSSION

Bulatao and Carlson, in 1924, demonstrated in the experimental animal, that hypoglycemia was accompanied by increased tonus and hypermotility of the stomach. In the same year, Dickson and Wilson reported this observation in the human. The hypoglycemia in both of these observations was produced by the subcutaneous administration of insulin. The increase in depth and rate of peristalsis and the rapidity of emptying of the stomach began about one hour and ten minutes after the administration of insulin. It continued for about two hours. Quigley, Johnson and Solomon made the same observation on four humans. They, however, reported to have found the action of insulin on the stomach to continue for four or five hours. Furthermore, they also demonstrated that there was immediate relief of the increased peristalsis and hunger, when glucose was given. The impetus to the study of hypoglycemia in the clinic was initiated, really, by Seale Harris.

The remarkable constancy of blood sugar in the normal animal is evidence of the sensitive equilibrium which exists between production, storage and utilization of sugar. Though a good deal has been said and written on the subject of glucose synthesis and oxidation, unfortunately exact knowledge of these chemical processes is not at hand. The conversion of glucose into CO_2 and H_2O is of extreme interest and yet very complex. The reason is that what is duplicated in the test tube is undeniably different from what actually goes on in the body.

While we know of the conversion of amino-acids into carbohydrate, we are not yet certain of the extent to which fat plays its role in the production of sugar in the animal.

It is firmly established that the liver plays a most vital role in the synthesis and utilization of sugar. It is, therefore, natural that disease or destruction of liver cells would be the most important factor in the diminished sugar content of the blood. A second, and very important factor, is the too rapid absorption of sugar from the blood by the tissues after extreme exertion or in the severe and rapid catabolism in febrile conditions. A combination of both of these factors may bring about a very severe and even fatal form of hypoglycemia. A less important, and yet existing possibility, is the faulty absorption of glucose from the gastro-intestinal tract, as in disease, such as diarrhoeas and cholera, etc.

The foregoing bio-chemical processes have been shown conclusively not to be self-regulating mechanisms. On the contrary, the normal functioning of the pancreas, pituitary, thyroid and adrenal cortex and medulla, are known to take part in the proper maintenance of a normal blood sugar. Thus it will be seen that the occurrence of hypoglycemia in an

individual is an indictment against the proper functioning of one of several organs, or a combination of them. The problem is intricate, requiring exhaustive study of all these organs, in order to gain additional evidence for the intelligent understanding and management of an existing hypoglycemia.

I have not elaborated on the disturbance of carbohydrate metabolism as it occurs in disease of the central nervous system. Stimulation of the floor of the fourth ventricle (Claude Bernard) and the hypothalamus are known to cause disturbed carbohydrate metabolism, experimentally. Yet the subject is too delicate and not sufficiently understood to go into at this time.

Now, as to a discussion of the cases under consideration, it will be correctly questioned whether a fasting blood sugar of 90 or 97 may be considered as abnormally low. To this, we must reply that the determined blood sugar in a fasting individual in a resting, basal state, is not a pertinent criterion of existing abnormality in carbohydrate metabolism. Much more decisive and revealing is the response of the body mechanism to the ingestion of a given amount of glucose. We know well what the established criteria are, for normal individuals, in such a procedure. Normally, the ingestion of a given amount of glucose by mouth, shows a rise in the blood sugar within several minutes. This rise is gradual, reaching its highest peak (usually 250 to 300 mgms. of sugar) at the end of two hours and returning to its normal level at the end of three hours. A substantial deviation from this classic graph may be interpreted as abnormal. In diabetes, we have a steep rise to about 300 in one hour, or less; the maintenance of this high level for about one or two hours, and the gradual tapering down to above normal by the end of three, four, or five hours. In increased sugar tolerance, or hypoglycemia, the reverse is true. After the ingestion of sugar, we see a small and gradual rise and, then, a rapid return to below normal at the end of two or three hours. Sometimes, there may not be any rise, or there may even be a fall in the blood sugar, giving a mirror image of the normal — a so-called paradoxical sugar tolerance curve.

It will be seen, then, from a study of the sugar tolerance curve, that an abnormal curve may reflect (1) the state of absorption, (2) the efficiency in the storage and liberation by the liver, (3) the utilization of sugar by the tissues. In our case, the interpretation of the curve may suggest either an avidity of the liver for sugar storing with resistance to replenishing the blood stream, or gluconeogenesis. Or it may signify an over-rapid utilization of the sugar in the blood stream by the muscles and tissues, and a sluggish response on the part of the liver to replenish the blood sugar. It may mean that the sensitive balance between utilization and production in maintaining a normal blood sugar is disturbed.

To further examine the problem, a determination of the basal metabolic rate disclosed a reading of minus

24%. This reading reflected the sluggish state of the thyroid. Since thyroxin is an insulin inhibitor, a diminution in the thyroxin is an insulin inhibitor, a unbridled action of insulin. Consequently there resulted a rapid removal of glucose by the muscles and tissues, too rapid for the normal liver to compensate by gluconeogenesis. That this interpretation is probably correct, can be deduced from the patient's disclosures that exercise, or augmentation of tissue oxidation, brought on the symptoms of hypoglycemia most precipitously, while rest and inactivity prevented the occurrence of symptoms.

Undoubtedly, many will find it hard to reconcile the fact that in some patients hypoglycemic symptoms arise at a very slight reduction in blood sugar while other individuals sustain marked reduction in blood sugar with no hypoglycemic symptoms. This apparent paradox is often met with in practice. It may be explained, perhaps, by the same variability which exists in diabetic individuals. There are many diabetics with a blood sugar of 300 to 500 who do not display any symptoms, and yet there are those who have a blood sugar of 250 and have most marked symptoms. The answer is not clearly known. One thing is certain, that a response to a drop in blood sugar is an individual factor. It varies with each individual. It is true that a sudden small drop will bring on symptoms more violently than a gradual and steep drop. It is probably dependent upon the adjustment mechanism of the body.

To prove the concept that in some individuals hypoglycemic symptoms may become apparent at a relatively high sugar level, and that these patients have a relatively high blood sugar threshold, it was decided to give the patient insulin and reduce his blood sugar gradually. By frequent blood sugar determinations after giving the insulin, and observation of the patient's behaviour clinically, at these blood sugar levels, we could determine two things: first whether a lowering of the blood sugar was responsible for symptoms complained of; second, at what blood sugar level these symptoms evidenced themselves.

From a study of the chart recording the blood sugar levels and the behaviour of the patient after insulin administration, it will be seen that the administration of insulin reproduced the exact symptoms the patient disclosed in his history, and that these symptoms appeared at a blood sugar level higher than that which is accepted normally. Furthermore, administration of sugar brought about after five minutes a disappearance of symptoms with the concomitant rise in the blood sugar. It seems obvious, then, that this simple test has proven conclusively that we were dealing with a patient who developed symptoms of hypoglycemia at a relatively high blood sugar level.

It is surprisingly little known by clinicians that such a high blood sugar threshold may actually exist in some patients. A moderate drop of the blood sugar

below this threshold level may apparently precipitate symptoms of hypoglycemia.

The poor synthesis of hippuric acid by the liver is interpreted as a reflection of the dysfunction of this organ. In the face of a normal galactose tolerance test, one must be cautious in concluding such a state. However, taken together with the evidence of impaired function of the thyroid, it suggests the possibility that dysfunction of the liver and thyroid may both play a part in the abnormal tolerance to sugar. In the face of inadequate and conflicting information regarding the role of both the thyroid and the liver in the maintenance of a normal sugar tolerance, it will serve no purpose to go into a polemic on this subject. Our interest, mainly, is the establishment of a relationship between symptoms of periodic abdominal pain, apprehension, fatigue, nervousness, air hunger, tremor, light-headedness, etc., and hypoglycemia. A recognition of this fact may help us understand such entities as the peptic ulcer syndrome with negative roentgen-ray findings, neurocirculatory asthenia without evidence of cardiovascular lability, and some confusing cases of psychoneurosis.

The use of the term hypoglycemia is usually restricted to the severe symptom complex associated with a marked and precipitous drop in the blood sugar content beyond that considered normal. Such clinical states are usually the result of large doses of insulin given to patients with diabetes. Occasionally, it is seen in an individual whose pancreas contains multiple or single, benign or malignant adenomata of the islands of Langerhans. Sometimes only a diffuse hyperplasia of the islet cells is found to be the cause of such hypoglycemic states. Furthermore, because of the close relationship and undoubted influence of the liver, adrenals, thyroid and pituitary glands in the maintenance of normal carbohydrate metabolism, the pancreas itself may be entirely innocent in the production of hypoglycemia states. Insufficiency or disturbance in the carbohydrate regulating factors in these glands may very well be responsible for the abnormality in the regulation or maintenance of a normal blood sugar.

A definite and more detailed understanding of the clinical picture of hypoglycemia has been gained since Sakel's insulin treatment of schizophrenia. In these observations, it was disclosed that the brain and central nervous system is the most dominant organ affected by the disturbed sugar content in the blood. Since the brain depends exclusively on carbohydrate for its energy supply, it can be readily seen why it is so predominantly affected.

The symptoms in the severe states of hypoglycemia may be seen to occur in stages, each stage corresponding to the level of the brain and central nervous system that is first affected. Thus we see, first, signs of cortical irritation and cerebellar involvement, tremor, loss of strength due to hypotonia, profuse sweating, confusion in orientation, speech, percep-

tion and thinking. Motor irritability is also sometimes seen.

The second stage involves a complete depression of the cerebral cortex, and an uninhibited release of the basal ganglia results. Such symptoms as athetoid, choreiform, clonic, hemiballistic movements and forced grasping occur in this stage. There are also signs of hypothalamic release with symptoms characterized by dilatation of the pupil, proptosis, increased heart rate, and other symptoms of sympathetic activity.

The third stage occurs with the depression of the higher basal ganglia, and release from control of the lower level, mesencephalon. In this stage, torsion spasms and convulsive seizures may take place with the eyes moving independently of each other.

The fourth stage begins with the depression of the above three levels and the picture of decerebrate rigidity sets in. Extensor spasms and periodic extension of all four extremities occur at this time. The arms are brought back over the head and the fingers are held in tetany. In this stage, the parasympathetic preponderates because of the control by the medulla oblongata. The heart rate is slow and the pupils are pin-point and somatic reflexes are depressed. When sugar is administered at this point, the picture is reversible and the patient can be brought back to normal. Disregard of this point produces cerebral anoxia with depression of the respiratory center and death.

The purpose in reviewing the symptoms of what is commonly understood to be the clinical syndrome of hypoglycemia, is to point out that there are mild forms of the clinical picture of hypoglycemia which are usually overlooked, because of the absence of dramatic and profound symptoms found in the severe hypoglycemic shocks. The milder symptoms are associated with a relatively small drop in the blood sugar level, at a relatively high threshold. In this latter form, the symptoms are bizarre and indefinite and very vaguely resemble other disease states.

Let us consider apart such symptoms as nervousness, tremors, weakness in the legs, fatigue, gasping for breath, pallor, cold perspiration, palpitation, slight mental dullness as well as periodic pains in the stomach relieved by food. All of these, separately or grouped together, are very unrevealing as to their possible underlying pathological cause. One could very justly consider these symptoms as the vague entity known as the DeCosta syndrome, or, in modern terminology, as neurocirculatory asthenia. Psychoneurosis, or even peptic ulcer with nervous symptoms may rightly be considered as possible diagnosis.

The striking similarity between the history of postprandial pain in peptic ulcer, and the hunger pain in contraction in hypoglycemia is still further confused by the response of both to food administration. Only an absence of the ulcer findings on X-ray examination, and the corroborative disclosure of a low blood sugar or, even better, an increased sugar tolerance

with low or flat curves, reveals the true underlying pathology. Thus, it is apparent that a patient presenting himself with an ulcer syndrome, in whom repeated X-ray studies reveal no evidence of ulcer, should be studied with a view to determine the state of his carbohydrate metabolism.

As to the necessity for studying the carbohydrate metabolic efficiency in the all-inclusive disease group known as neurocirculatory asthenia — or effort syndrome, or difficult action of the heart, a comparison of symptoms disclosed by a patient with mild hypoglycemia, or increased sugar tolerance, and the symptoms included under the syndrome of neuro-circulatory asthenia, attest to the almost identical nature of the symptoms in these two syndromes.

When neither neuro-circulatory asthenia, peptic ulcer, or carbohydrate disturbances is suspected, the ultimate abandonment of the patient to the psychiatrist is inevitable, for without a substantial explanation of his symptoms, one hopes, in sheer desperation, that the psychiatrist can perform the miracle of curing this patient. This, of course, is a very disappointing wish.

When the sugar tolerance test is not decisive, an attempt should be made to reproduce the symptoms by the injection of 10-12 units of insulin, followed an hour and 15 minutes later by another injection of 20 units. By noting the level of the blood sugar at which subjective and objective symptoms appear, one can determine the individual's threshold for glucose below which symptoms of hypoglycemia appear. It is even possible to bring on these symptoms by subjecting the patient to vigorous exercise, during which the available blood sugar is rapidly removed from the blood stream and the symptoms of mild hypoglycemia similarly reproduced.

The study of this group of individuals as hitherto discussed is further justified by their response to treatment. Based on the physiologic observations of Mehring and Minkowski "that the internal secretion of the pancreas is inversely proportional to the external secretion," these patients when placed on a high fat and protein diet, show a remarkable improvement and amelioration of their symptoms. Simultaneously, the blood sugar tolerance curve will often show a tendency to revert to normal. If necessary, the individuals may be advised to resort to extra small feedings in between meals. In this way, the blood sugar level is kept above the critical level below which symptoms of hypoglycemia appear.

SUMMARY

1. Four cases are presented in which vague symptoms of a bizarre character were experienced for four years. In some, there is a family history of similar complaints.
2. These symptoms were: nervousness, palpitation, apprehension, weakness in the legs, tremors, excessive perspiration, mental dullness and hunger pains relieved by food.

3. The symptoms were aggravated or precipitated by physical effort and were prevented or relieved by eating and rest.
4. The similarity of the group of symptoms, to symptoms associated with peptic ulcer, neuro-circulatory asthenia, or psychoneurosis is discussed.
5. The disclosure of the true cause for these symptoms by a study of the sugar tolerance, suggested itself from the similarity of these symptoms to those of hypoglycemia.
6. Study of the blood sugar level at which symptoms of mild hypoglycemia occurred, revealed that these patients displayed symptoms at a relatively high sugar level. The implication of this observation is discussed.
7. Confirmation of the observation that these patients' symptoms are due to relative hypoglycemia, was revealed by reproduction of the same symptoms with insulin and exercise. At a relatively high blood sugar level (88 mgms. per 100 cc.) one patient began to have symptoms as tremor, air hunger and a peculiar discomfort in the pit of his abdomen. More severe symptoms were evident at 74 mgms. of blood sugar. A disappearance of symptoms took place with the administration of orange juice.
8. The value of a high fat and high protein diet in the prevention and relief of this metabolic disturbance is discussed, as is the physiologic principle upon which this treatment is based.
9. The practical value of the search for this entity in such obscure diseases as neurocirculatory asthenia, psychoneurosis, and peptic ulcer syndrome without positive X-ray findings, is discussed.
10. The role of the liver and thyroid efficiency in the maintenance of a so-called normal sugar tolerance is mentioned. These patients disclosed mild liver and thyroid dysfunction. No attempt has been made to discuss the bearing of these findings on the underlying carbohydrate tolerance.
11. The concept that mild symptoms of hypoglycemia may appear at a relatively high sugar level is stressed.

Recognition of this fact has been recently expressed in several articles. However, this fact is not universally recognized though it deserves widespread recognition. Just as in the anemias, a sudden drop of the hemoglobin and RBC to 60% of normal may precipitate a dramatic train of symptoms and even shock — while a slow and gradual drop of hemoglobin and red blood cells to as low as 20% of normal may be borne with relative impunity by the patient. Undoubtedly, such an observation applies to many other physiologic and chemical phenomena in the animal economy. It is important to remember then,

that a sudden, small alteration in the sugar level of a human being may precipitate severe symptoms of hypoglycemia, while a relatively large drop in the blood sugar to a level as low as 40 mgms. per cent, occurring slowly, may be borne by an individual without displaying a single symptom of such a state. The explanation for this paradox unquestionably lies in the adjustment mechanism of the animal economy. Hans Selye's work — on the physiology of adaptation — may very well be applicable in such instances.

I have intentionally avoided a physico-chemical discussion of the sugar tolerance curve, or glucose

metabolism. I leave that to the experimental physiologist who would be more at home in that field. It is my purpose, in citing these cases, to provoke the medical profession into considering the role of glucose tolerance and relative hypoglycemia when confronted by an obscure case presenting a symptom complex identical with peptic ulcer, neurocirculatory asthenia, and psychoneurosis. It is hoped that a further study of this condition will reveal its frequency and its relation to the aforementioned symptom complexes.

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Editorials

FISH POISONING AT FANNING ISLAND

BETWEEN FEBRUARY 1946 and April 1947 there were 95 cases of fish poisoning* at Fanning Island; which lies in the Central Pacific, approximately 1500 miles south of Hawaii, among a total population of 224 people on the Island, whereas previously no fish had been definitely found poisonous except the "balloon fish." Now at least 10 species of fish have become poisonous as a direct result of contamination nearby caused by the dumping of discarded war materials by the United States Army. At first the symptoms were largely gastro-intestinal but during the past two years, according to Dr. Ross, there has been added a somewhat serious neurotoxic factor, causing numbness in the limbs, facial tingling and

vertigo. Clinically the disease is characterized by bradycardia, contracted pupils and a feeling of coldness in the extremities when they are immersed in water at room temperature. Recovery is very gradual and weakness persists for several weeks. Just how the fish became poisonous is not definitely known but presumably metallic poisons as well as a strychnine-like alkaloid gradually develop in the sea-water as a result of contamination by dumped war materials, the poisons being taken up by the plankton and algae on which the fish feed. Treatment consists in purgation, gastric lavage, rest and supportive tonics. Whether this instance of fish-poisoning represents something new in pathology, wherein a poison of metallic nature passes through an intermediary edible "host" is uncertain, but it may possibly be prophetic of similar disease resulting in the future directly from water, or even air contamination, through the activities of war.

* Ross, S. G.: A Preliminary Report on Fish Poisoning at Fanning Island (Central Pacific). Med. J. Australia, Nov. 22, 1947, Vol. II, No. 21, 617-621.

FREUD AND PSYCHOANALYSIS

THE RECENT DEATH of Sigmund Freud, M.D. has removed from human society the most incisive medical psychologist of all time and one of the greatest Jews in history. The perspective of the past four decades reveals the unique value of his work and himself as the investigator laying no conscious claim to philosophy. He dissected human personality along one of its lines of cleavage so faithfully that he is forgiven if he overlooked other lines, thought by many to exist.

The "psychology of error" was a concept fraught with radical implications for normal and abnormal studies, and formed the foundation along with dream analysis, for the investigative and therapeutic procedures erected thereon by Freud, by his disciples and others, who, while recognizing the value of his methods, could not follow him all the way.

The concept of the *libido* is invaluable in assessing the dynamics of personality, but restriction of the term to "sexual drive" was not approved by many eminent and objective psychiatrists such as Jung, who nevertheless hailed Freud as the father of psychoanalysis. To say that the Unconscious contained *nothing except the sexual drive* was a tactical error and a gross presumption which cost Freud heavily in prestige even among his medical brethren to this day. Naturally, his biological characterization of the Unconscious ran counter to the tenets of churchmen in general and became irritating even to many rational idealists.

It is easy enough to condense the case against Freud, as it appears in the somewhat altered moral consciousness of the past three decades. His views on *narcissism* are not understood as applicable to the unfolding infantile mind but are taken as a cynical rebuttal of human unselfishness. His interpretation of dreams as wish fulfillment, while not challenged on that ground, omits the prophetic significance of dream imagery as scientifically introduced by Dunne. In general, there is opposition to a descriptive system which hangs the beginning and therefore the end of man on the two horns of a *love-love object* dilemma. This was all Freud confessed finding, but did he really look for other motivations? Is man actually a plethora of all conceivable energies, so that any investigator may find exactly what he is searching for? If we catch only devil-fish in the ocean, does that mean that no other kinds of fish exist, or does it mean that we are using only one sort of bait? Whether these questions actually impugn Freud's objectivity cannot be stated, but they represent the only logical elements in the public's adverse attitude.

The rest is pure and elemental emotion. Freud himself was always aware of the almost insuperable antipathy which he aroused in the laity. It is a tribute to his genius for persistent propaganda that he was not trampled in the dust and long since forgotten. There is nothing more savage than an outraged public and yet nothing more potent than patient and logical education. Even today most persons regard Freud as an impudent interloper within their secret

shrine, and he is spurned with the same truculence that is visited by tribesmen on those who have violated the tribe's most sacred Tabu. Perhaps for that very reason he can never become a truly popular figure.

The ultimate fate of psychoanalysis will depend upon the general attitude of Freud's followers and the public's reaction, but essentially upon the level of helpfulness which the craft attain. The movies and current fiction, while overplaying the subject to the point of nausea, are making it coherent for the first

time to the public — and as a result there is an increasing tendency to consult the psychiatrist.

It is eminently fair to credit Freud with a unique stimulation of psychological attack and with unprecedented progress in the treatment of the neuroses, even though his method remains ineffectual in the psychoses. His contribution to descriptive biology is classical and fundamental and the name of Sigmund Freud will endure as long as human culture.

Book Review

SHOOT THAT NEEDLE STRAIGHT. By Robert Rantoul, Pp. 220, (\$2.75) Bruce Humphries, Inc., Boston, 1947.

This is a book that might safely be presented by a physician to a diabetic patient or by anyone to a friend suffering from the disease. The style is brisk and engaging and the story describes the mental and

physical experiences of a young man from the beginning of his symptoms, through his medical treatment and education at the hands of a high-grade ethical physician to his unfortunate encounter with a criminal quack and beyond that, through many interesting experiences of his life. The general dietary regimen and the insulin therapy are described in exemplary fashion.

Abstracts Of Current Literature

ABSTRACT EDITOR — M. H. F. FRIEDMAN

Jefferson Medical College

1025 Walnut Street

Philadelphia, Pennsylvania

CLINICAL MEDICINE

MOUTH AND ESOPHAGUS

LONG, D.A.: *Effect of penicillin on bacterial flora of the mouth.* (Brit. Med. J., Nov. 22, 1947, 819-820).

Either the local application of penicillin to the mouth or the systemic administration of penicillin in large doses profoundly affects oral bacterial, but only in systemic treatment is the flora of the tonsils, pharynx and nose affected. Excretion of penicillin in the saliva probably only occurs when doses of more than 500,000 units per 24 hours are used. It can be demonstrated only in the initial phase of reduction of bacteria before gram-negative bacilli become established. The latter produce sufficient penicillinase to destroy it.

CUNHA, F.: *Achalasia and megaesophagus as a complication and sequella of pertussis.* (Rev. Gastroenterology, Oct. 1947, Vol. 14, No. 10, 693-704).

A case is reported of a man of 44 who complained of fullness and heaviness in the chest, sometimes transmitted upward into the neck. Examination led to a diagnosis of achalasia and megaesophagus. The patient had recently experienced a severe illness with pertussis and the idea is advanced that a toxic lesion of a portion of Auerbach's plexus led to true idiopathic dilatation of the esophagus. The patient did not complain of difficulty in swallowing.

PANCREAS

HERRMANN, S. F.: *Surgery of the pancreas.* (Northwest Medicine, Oct. 1947, Vol. 46, No. 10, 770-772).

A review of surgical treatment of pancreatic cysts, acute pancreatitis, injuries to the organ, hyperinsulinism, and cancer. Total pancreatectomy is being successfully done — resultant metabolic changes are readily controlled. The pancreas is no longer indispensable.

BARTONER, R. R. AND COLLINS, E. N.: *Chronic relapsing pancreatitis*. (Cleveland Clinic Quarterly, Oct. 1947, Vol. 14, No. 4, 230-238).

The authors draw attention to chronic relapsing pancreatitis and show its resemblance to acute pancreatitis. Steatorrhea, diabetes and pancreatic lithiasis are among the major diagnostic criteria. They review 19 cases of primary chronic relapsing pancreatitis with no intercurrent or associated disease. The medical and surgical treatment is described.

ULCER

WALTERS, W.: *Vagotomy for peptic ulcer*. (Proc. Staff Meet. Mayo Clinic, Vol. 22, p. 281, July, 1947).

Up to the beginning of 1947 the author performed 40 vagotomies for peptic ulcer. An additional 40 vagotomies were performed at the clinic by other surgeons during the same period. These 80 operations may be divided as follows: I — Vagus section for 16 cases of duodenal ulcer, 14 gastrojejunal ulcer, 2 gastric ulcer, II — Vagus section combined with gastroenterostomy for 30 cases of duodenal ulcer, and III — Vagus section with excision of the ulcer for 5 cases of duodenal ulcer, 10 gastrojejunal ulcer, 3 gastric ulcer and 1 gastritis.

When gastroenterostomy alone was performed, a relative achlorhydria occurred in 12 per cent of the cases; this was raised to 50 per cent when vagotomy was added to the gastroenterostomy. A few patients developed prolonged gastric retention. One patient with vagotomy and gastroenterostomy experienced retention for 26 days and required jejunojejunostomy. Two of the patients had distressing diarrhea. In one patient following complete vagotomy and excision of a gastric ulcer there was recurrence of the ulcer: gastric resection was required.

The author concludes that vagotomy is still in the stage of clinical investigation but already we know that it does not have a place in treatment of chronic gastric ulcer.

M. H. F. Friedman

AVENT, C. H., PATTERSON, R. H. AND CHAMBERS, J. M., Jr.: *Acute perforated gastro-duodenal ulcer*. (Southern Surg., Vol. 13, No. 9, Sept. 1947).

A review of case histories of 129 patients with acute perforated gastroduodenal ulcers admitted to John Gartin Hospital from Jan. 1, 1940 to Jan. 1, 1947. All patients reviewed required surgery and the corrected mortality rate was 10.1 per cent. This rate was directly proportional to the number of hours

intervening between perforation and closure. The mortality rate was lower in those patients having no previous symptoms and in those with symptoms which had been present for more than one year. A leukocyte count preoperatively of less than 6,000 meant a poor prognosis. A sex and race differential showed an incidence of seven colored men to nine white men and two colored women to five white women.

J. Meadoff

STEIN, I. F., JR., STEINMANN, F. AND MEYER, K. A.: *Studies of gastric motility on ulcer patients before and after vagotomy — effect of parasympathomimetic drugs*. (Federal. Proceed., Vol. 6, p. 374, March 1947).

Fifteen patients were studied following vagus section. Gastric motility studies were made before and after operation. The results of the vagotomy were such as to increase emptying time and produce retention for four to six or more hours.

Prostigmine, 30 mg. orally or 0.25 to 0.50 mg. subcutaneously, was ineffective in increasing the post-operative gastric motility. Doryl, 0.25 mg. subcutaneously or two mg. orally, and Urecholine, 10 mg. orally, produced marked increase in gastric motility. The authors believe these two drugs may be useful for relieving the gastric atony of vagotomy.

J. S. Moffitt

JONES, F. A.: *Hematemesis and melena — with special reference to bleeding peptic ulcer*. (Brit. Med. J., Sept. 27, 1947, 477-485).

From a study of a large series of hospital cases, the chief finding of pure clinical interest was to the effect that bleeding ulcer actually carries a considerable mortality (eight per cent) in spite of fallacious theories to the contrary. Associated complications, giant ulcers and old age are important factors contributing to death. The author favors drip blood transfusions and early feeding. Gastroscopy makes the diagnosis when the bleeding is from an acute ulcer.

A test for the presence of duodenal ulcer: (Reprinted from Med. J. Australia, June 28, Vol. 1, No. 26, 792).

The diagnosis of duodenal ulcer and the determination of whether or not healing is complete still offer problems. Radiographic evidence is sometimes equivocal and normal findings do not always indicate that an ulcer is not present or that an ulcer previously demonstrated is healed. The gastroscope has proved a useful addition to the investigation of gastric ulcer,

but difficulties are greater in the case of the duodenum. A useful test has recently been suggested by Andrew W. Kay¹ based on the effect on gastric motility of the introduction of cold water into the stomach. Following the work of Carlson (1916) and Anderson (1943), Kay recorded the effect of introducing cold and hot water and also saline solution of varying strengths into the stomachs of normal subjects as well as of those suffering from various dyspeptic conditions. The gastric motility was recorded by means of a swallowed balloon inflated to a standard pressure of ten centimetres of water and a tambour-kymograph unit. The principal findings were that the ingestion of cold water by normal subjects inhibited normal gastric contractions, but that in the presence of a duodenal ulcer gastric contractions were either normal or increased; these findings occurred consistently in 30 normal subjects and in 90 subjects who had a duodenal ulcer radiographically demonstrated. Hypertonic saline solutions inhibited gastric contractions in subjects with duodenal ulcer. In subjects whose ulcer could be reasonably regarded as healed, ingestion of cold water produced inhibition. Cold water produced a normal response (inhibition) in 33 of 34 patients suffering from definite organic disease of the stomach (ulcer 12, carcinoma 22). The one patient in whom inhibition was not produced was suffering from gastric carcinoma which had invaded the duodenum. Of nine patients suffering from acute cholecystitis, in two the water test excited gastric contractions; in one of these laparotomy revealed an empyema of the gall-bladder with adherent duodenum; the second instance was unexplained. The broad conclusion of these experiments is that, in the presence of duodenal disease, the ingestion of cold water does not inhibit gastric motility as it does in a normal subject. Bearing in mind the rare occurrence of a carcinomatous involvement of the duodenum and the possible occasional fallacy due to gall-bladder disease, the water test should be of value in deciding the presence or otherwise of a clinically active duodenal ulcer. This will be of use not only in diagnosis, but also in determining when healing has taken place. The gastroscope has shown unhealed gastric ulcers where clinical and radiographic evidence all indicated that healing was complete. The water test, which is apparently simple and no more unpleasant to the patient than a gastric test meal, should help to fill the existing gap in our facilities for assessing the condition of the duodenum.

MEYER, K. A.: *Recent surgical advances in the treatment of ulcers of the duodenum.* (J. Ind. State Med. Assoc., Oct. 1947, Vol. 40, No. 10; 986-987).

Clinically, what is the effect of vagi section on gastric secretion and on gastric motility? It is this. The average normal individual, when tested from 8:00 o'clock at night to 8:00 o'clock in the morning will have a secretion of about 300 cc. of gastric juice of normal free acidity and normal combined acidity. The individual with duodenal ulcer will have a high night secretion, two to three times the normal secretion. That is also the reason why Sippy taught his men and his patients to use the Ewald tube; in other words, they aspirated themselves and never allowed the secretion to accumulate. With a hypersecretion there is hypermotility, hyperacidity, and night distress. Consequently, reduction of hypersecretion reduces the other factors also. In other words, if a man has a thousand cc. of high acid retention at night, and a vagi section is done, his secretion will go down to 200 or 300 cc. of normal acid gastric juice, and undoubtedly that plays the greatest factor in the ulcer problem. This again bears out the teaching of Sippy, that it is the acid factor that is the important factor in the treatment of ulcer. Vagotomy also stops hypermotility and one will observe a much slower emptying of the stomach by X-ray.

LIVER AND GALLBLADDER

WISE, B. L. AND ESKWITT, H. M.: *Cirrhosis of the liver in childhood (report of a case in a nine year old).* (Arch. Pediat., Dec. 1947, Vol. 64, No. 12, 638-648).

Cirrhosis of the liver is uncommon in children. A fatal case in a boy of nine is described. Ascites, pre-tibial edema, petechiae on the arms and terminal fever with wasting were the chief symptoms. At autopsy the liver showed thickened bands of connective tissue redividing the liver into irregular nodules. The connective tissue was infiltrated by mononuclear, chronic inflammatory cells, lymphocytes and plasma cells. The final diagnosis was portal cirrhosis and bronchopneumonia. The authors present a new classification for hepatic cirrhosis.

RABY, A. K. AND WANSCHER, O.: *The interrelation between ventricular and hepatic disease.* (Nordisk Med., Oct. 10, 1947, Vol. 36, No. 41, 2049-2050).

In 32 patients, most of whom suffered from heart disease, the heart and liver were subjected to formalin

(1) American Journal of Diseases of Children, March 1947.

fixation immediately after death. Microscopic examination of the livers showed interstitial inflammatory changes in 18, amounting in some cases to portal cirrhosis. Among 78 patients without clinical evidence of heart or liver disease, 57 were without pathological post mortem changes in the liver. It is inferred by the authors that ventricular heart disease may produce liver changes by interfering with normal digestion and absorption of food.

DARMSTAETTER, A. A., BLAIN, J. H. AND LOFSTROM, J. E.: *An evaluation of the accuracy of cholecystography*. (Alexander Blain Hosp. Bull., Nov. 1947, Vol. 6, No. 4).

The presence of gallstones at operation must be regarded as the best criterion of a pathological condition of the gall bladder, because, although many noncalculous gallbladders are diseased, too much reliance cannot be placed on pathological reports, in making a statistical review. Priodax is regarded as the contrast medium of choice. Where good gall bladder function was indicated by X-ray, stones were found at operation in 14.3 per cent of cases. Where gall bladder function appeared to be absent, stones were found at operation in 63.4 per cent of cases. In cases in which no gall stones were visualized by X-ray, stones were found at operation in 51.2 per cent of cases. It was shown that clinical judgment was just as accurate in 25 per cent of the operated cases who had no X-ray study, as in the 75 per cent who were subjected to cholecystography, prior to surgery. The study suggests that the incidence of good gall bladder function decreases with age and the incidence of stones present at operation increases. Between ages 25 and 65, there is 30 per cent discrepancy between stones found by X-ray and those found at operation. (It has been suggested that the poor visualization of gall bladders seen in peptic ulcer patients may be due to the increased production of cholecystokinin, which has a cholegogue action).

BOGGS, E. F.: *Cirrhosis of the liver: prospects for earlier diagnosis and treatment*. (J. Indiana State Med. Assn., Sept. 1947, Vol. 40, No. 9, 858-863).

Among the early diagnostic indications and procedures in cirrhosis, the author lists gastro-intestinal upsets, presence of esophageal varices, gastric vascular lesions, diminished size of the liver, hydrothorax, increased splenic shadow, infra-red illumination and photography of the torso, peritoneoscopy and liver biopsy.

QUICK, A. J.: *Pancreatic and liver function*. (Northwest Medicine, Oct. 1947, Vol. 46, No. 10, 762-764).

This article reviews various features of the title subject but devotes special attention to detailing the merits and advantages of the hippuric acid test of hepatic function, a test which Dr. Quick himself devised. He outlines its significance under varying clinical conditions.

BROWN, B. A.: *The differential diagnosis of jaundice*. (Northwest Medicine, Oct. 1947, Vol. 46, No. 10, 765-770).

Another useful, critical evaluation of the tests and means at our disposal for determining the cause of jaundice.

MACLAGAN, N. F.: *Liver function tests in the diagnosis of jaundice (review of 200 cases)*. (Brit. Med. J., Aug. 9, 1947, 197-201).

The results obtained in 200 cases of jaundice with the serum alkaline phosphatase, thymol turbidity, thymol flocculation, and serum colloidal gold tests are analysed in relation to their diagnostic value.

The combination of phosphatase with one flocculation test will distinguish obstructive from non-obstructive jaundice in from 65 to 79% of cases. The thymol flocculation test is slightly the best of the three flocculation tests tried.

Diagnostic criteria are given for the various tests. Strongly positive flocculation reactions or phosphatase levels below 15 King-Armstrong units suggest non-obstructive jaundice; negative or weakly positive flocculation reactions with phosphatase levels above 35 units suggest biliary obstruction, and phosphatase levels above 42 units are also in favor of obstruction.

UPHAM, R.: *Jaundice*. (Rev. Gastroenterol., Nov. 1947, Vol. 14, No. 11, 775-786).

A lucid discussion of the diagnosis of jaundice which follows Rich's classification, largely. The author emphasizes the fact that each instance of jaundice presents a problem of its own.

FALOMIR, J. M. AND HUGHES, C. R.: *Carcinoma of the pancreas (with special reference to the body and tail)*. Cleveland Clinic Quarterly, Jan. 1948, Vol. 15, No. 1, 30-35).

In cancer of the body and tail of the pancreas, the common and most important symptoms are pain with characteristic radiation to the back and severe loss of weight. Jaundice is a prominent symptom only in cancer of the head of the pancreas. X-ray evidence of extrinsic pressure on the stomach or duodenum is helpful in diagnosis.

STOMACH

CODOUNIS, A.: *Contribution to the study of the anemias associated with diaphragmatic hernias*. (Acta Gastro-Enterol. Belgica, June 1947, Vol. 10, No. 6, 345-365).

While it is recognized that both microcytic and macrocytic (hyperchromic) anemias may accompany diaphragmatic hernias, the author presents a case in which the characteristics of the blood picture fluctuated between these two extremes from time to time. Our lack of knowledge in this subject is largely due to the fact that hematologists do not look for diaphragmatic hernias and surgeons, recognizing this anatomical condition, are not especially interested in a possible associated anemia. Radiological studies frequently show diverticula of the body of the stomach and the descending portion of the duodenum in cases of diaphragmatic hernias. The blood and bone marrow should be examined in every case of diaphragmatic hernia.

SPENCER, F. M., COLLINS, E. N. AND RENSHAW, R. J.: *Sarcoma of the stomach*. (Cleveland Clinic Quarterly, Oct. 1947, Vol. 14, No. 4, 282-295).

The authors present 19 proved cases of gastric sarcoma. Two patients who have survived more than five years without evidence of recurrence were treated by a combination of surgery and roentgen therapy. This applies also to two cases living and well more than three years after treatment was begun. (The authors report a case of Frank E. Bant's who is still alive and well 31 years after operation). The authors emphasize that, not infrequently, these cases present symptoms suggestive of peptic ulcer — a fact which renders obvious the necessity of careful gastric X-ray examination. The chief X-ray findings were — hypertrophy of the gastric rugae, large irregular ulcerations, diffuse infiltration and the presence of single or multiple polypoid gastric neoplasms.

BOWEL

HOFFMAN, J. M.: *Tumor intussusception*. (Northwest Med., Dec. 1947, Vol. 46, No. 12, 950-953).

The author describes two cases of intussusception in which the ileum and cecum entered the ascending colon as a result of a tumor of the cecum. One was a benign papilloma and the other an adenocarcinoma. Both cases recovered after resection and anastomosis. This complication should be kept in mind in the management of bowel obstructions.

SHUN-SHIN, M.: *Balantidial dysentery in Rodriguez and its treatment with mercury biniodide*. (Brit. Med. J., Sept. 13, 1947, 417-418).

Ten cases of balantidial dysentery are described. The first case treated with mepacrine ended fatally.

The nine other cases, treated by intramuscular injections of biniodide of mercury, were cured, but one of them required in addition an enema of the biniodide.

It is suggested that intramuscular injection be used except when the protozoa are living also in the lumen, when injections combined with enemata are probably best.

HODGES, FRED JENNER: *X-ray demonstrable lesions of the colon*. (Illinois Med. J., November 1947, Vol. 92, No. 5, 279-282).

X-ray examination of the colon by the barium enema method is a practical and valuable diagnostic procedure which deserves wider application. About 75 per cent of patients so examined will be found to have no demonstrable colonic lesion. When X-ray examination is used widely, both in the face of leading symptoms and "on suspicion," one may expect to encounter important intrinsic organic lesions in the order of *once for every twelve patients investigated*.

WILLIAMS, H.: *Appendicitis in the young child*. (Brit. Med. J., Nov. 8, 1947, 730-732).

The reason appendicitis is not often enough diagnosed in the young child is a failure to suspect appendicitis at this age. The history is important and the clinical examination deliberate. Once the case is complicated by perforation, the same problem arises as in adults as to whether or not to defer laparotomy.

IRONS, W. E., JUDD, E. S., AND DOCKERTY, M. B.: *Endometrioma of the cecum*. (Proc. Staff Meet. Mayo Clinic, Nov. 12, 1947, Vol. 22, No. 23, 530-534).

The authors state that endometrioma involving the cecum is rare, only three cases having been encountered at the Mayo Clinic in twenty years. One of these cases is described. Usually the lesion is suspected of

being a carcinoma. Removal stopped menstrual and post-menstrual pain simulating appendicitis.

HODGES, F. J., RUNDLES, R. W. AND HANELIN J.: *Roentgenologic study of the small intestine. I. Neoplastic and inflammatory diseases.* (Radiology, Nov. 1947, Vol. 49, No. 5, 587-602).

Out of many patients whose complaints are referable to the small gut, a relatively small group show clearly defined roentgen signs of inflammatory and neoplastic disease, and it is never easy to separate organic from functional disease. A great deal can be learned however by a simple routine diagnostic procedure involving very little fluoroscopy but with serial abdominal films at stated intervals following the meal.

HODGES, F. J., RUNDLES, R. W. AND HANELIN, J.: *Roentgenologic study of the small intestine. II. Dys-*

function associated with neurologic diseases. (Radiology, December 1947, Vol. 49, No. 6, 659-673).

The patients studied were suffering from diabetes, pernicious anemia and tabes dorsalis (but only those cases which showed definite peripheral nerve degeneration or cord changes) as well as some cases of peripheral neuropathy of unknown causation, the Guillain-Barre syndrome, lead palsy and one case of autonomic nerve paralysis. Prolonged delay in gastric emptying and disorderly transit of barium along the intestinal tract was the chief finding and gave graphic evidence of autonomic nerve injury which improved markedly in diabetes once the cases were brought under therapeutic control and in pernicious anemia under the full influence of anti-anemic treatment. The X-ray studies in tabes did not reveal striking abnormalities. Following vagotomy, there was a tendency to softer stool and sometimes severe chronic diarrhea.

The Use of High Protein Diets in the Treatment of Diabetes Mellitus

By

DAVID ADLERSBERG, M.D., F.A.C.P.

NEW YORK, N. Y.

150TH ANNIVERSARY OF DIET THERAPY FOR DIABETES

THE TWENTY-FIFTH ANNIVERSARY of the discovery of insulin coincides with the one-hundred fiftieth anniversary of the initiation of diet therapy in diabetes. In 1796 John Rollo (23), a surgeon-general of the English army, inaugurated a diet system for the treatment of diabetes which consisted exclusively of animal food (see Fig. 1 & 2). His thirty-four year old patient, Captain Meredith of the Royal Artillery, had suffered for seven months from excessive polyuria (12 quarts of urine daily) and thirst, severe loss of weight and dry skin. The diet was ordered on October 16, 1796 (see Fig. 3) and had a remarkable result. Polyuria and polydipsia subsided, there was considerable improvement of the general condition and gain in weight. This diet system for many decades was the only treatment for the disease.

Because of the ease and efficacy of insulin therapy, its use increased considerably since its discovery, year by year, to the great advantage of those afflicted with the disease. On the other hand, one observes at present a tendency to somewhat neglect the dietary aspect of the treatment. Insulin exerts its beneficial effect irrespective of the diet used. Many of our younger diabetologists had no opportunity to familiarize themselves with the old science and art of diet therapy in diabetes, especially as it was practised in the pre-insulin era. Some authorities in the field consider dietotherapy of diabetes a dead art. We are inclined to believe that even at present only a combination of insulin and expert diet therapy renders optimal results. Many mild and moderately severe cases can be satisfactorily maintained without insulin by the proper application of dietotherapy.

HISTORICAL REVIEW

It may be interesting to briefly review the development of diet treatment of diabetes prior to the discovery of insulin. The favorable effects of Rollo's low-carbohydrate, high-protein and high-fat diet were confirmed by many authors (Bouchardat (6), 1851, Seegen (25), 1860, Pavy (19), 1878, Cantani (7), 1880, Naunyn (16), 1888). It was then established by Bouchardat, Cantani, and especially Naunyn, that protein being a source of sugar, may also be harmful. Towards the end of the nineteenth century, there was already a tendency to restrict the carbohydrate and protein intake in diabetes and to employ

larger amounts of fat. The beneficial effects of caloric restriction and fasting were recognized rather early by Bouchardat, Cantani, Naunyn and Von Noorden (18).

In this century, Guelpa (13) resorted to longer periods of fasting and Allen (3) developed a treatment based on prolonged starvation and systematic use of caloric restriction. Continuing Naunyn's observations that excess of proteins depresses carbohydrate tolerance, in 1920 Petré (20) in Sweden, and Newburgh and Marsh (17) in the United States, independently studied diets very low in carbohydrate and protein, and high in fat. Petré was able to maintain nitrogen equilibrium and prevent ketosis in his diabetic patients. Thus, the prevailing tendency twenty-five years ago was to restrict the caloric intake in diabetes and to cover it mainly with fat.

Besides this main road of diet therapy there were several less frequented side roads. Some authorities used individual foodstuffs in various "cures": Donkin's skimmed milk regimen, the rice cure (Duering (10)), the potato cure (Mosse (15)) and finally, the famous oatmeal cure (Von Noorden (18)). Von Noorden used alternately a few types of diets: A standard diet (low-carbohydrate, high-protein and high-fat) was followed by a day or two of a vegetable diet (low carbohydrate, low-protein and high-fat), and then by one or two oatmeal days (high-carbohydrate, high-fat and low-protein).

After the discovery of insulin the old types of diet remained in practice for only a few years. Severe dietary restrictions, especially fasting, and shifting and alternating diets, previously used, became unnecessary. Under the protection of insulin, a more physiologic type of diet everywhere came into use. This diet, according to various clinics, may be moderately limited in carbohydrates and proteins and fat.

HIGH-PROTEIN, LOW-FAT DIET

For over twenty years we have been interested in the use of high-protein diets for the treatment of diabetes (1, 2). The high-protein diets generally used in the pre-insulin era were heavily loaded with fat and were low in carbohydrate. The high-protein diets to be discussed are low in fat and contain moderate amounts of carbohydrate (about 100 gms.).

In experimental and clinical studies on the effect of dietary carbohydrate, protein and fat in the metabolism of normal and diabetic individuals, it was shown by Porges and myself (1, 2, 21) that excessive

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Thomson CASES OF THE *Broadhead*

DIABETES MELLITUS;

WITH

THE RESULTS

OF THE

TRIALS OF CERTAIN ACIDS,

AND OTHER SUBSTANCES,

IN THE

CURE OF THE LUES VENEREA.

BY

JOHN ROLLO, M.D.

SURGEON-GENERAL, ROYAL ARTILLERY.

SECOND EDITION,

WITH LARGE ADDITION.

LONDON:

PRINTED BY T. GILLET,

FOR C. DILLY, IN THE POLITRY.

MDCCLXXIII.

Fig. 1. Photostatic reproduction of the front page of John Rollo's monograph which introduced diet treatment in diabetes mellitus. (Second Edition)

amounts of fat resulted in impairment of carbohydrate tolerance. These studies were performed in short and long periods of iso-caloric nutrition in which the content of carbohydrate, protein and fat varied from limited to excessive amounts. They led us to the theory that the antagonistic effect of glycogen and fat on the liver may be an important factor responsible for improvement or impairment of carbohydrate tolerance in diabetes; a high glycogen content of the liver cells will enhance their capacity to store sugar while an excessive fat content will be effective in the opposite way.

On the basis of these studies a system of low-fat diets was introduced for the treatment of diabetes. The application of "physiologic alimentation" in severe cases of diabetes was made possible by the administration of insulin. The independent work of many students in the field (1, 2, 21, 11, 24, 22, 4, 14, 26) eventually resulted in "liberal" or "high carbohydrate" diet forms which at present are the basis of therapy in diabetes treated with insulin.

The application of a similar high-carbohydrate,

PART I.

CASES

OF THE

DIABETES MELLITUS;

WITH

A GENERAL VIEW

OF

THE NATURE OF THE DISEASE,

AND

ITS APPROPRIATE TREATMENT.

INCLUDING,

A CONCISE REVIEW OF WHAT HAS BEEN WRITTEN ON THE SUBJECT; AN ANSWER TO SOME OBJECTIONS UROED AGAINST THE DOCTRINE WE HAVE DELIVERED; AND CHEMICAL EXPERIMENTS ON URINE, AND SUGAR.

Fig. 2. Photostatic reproduction of front page of part I of John Rollo's monograph.

low-fat regimen to the non-insulinized diabetic met with difficulties because the ingestion of higher amounts of carbohydrate exerted an unfavorable effect on blood sugar level and glycosuria. The use of the low-fat regimen in these instances was possible by a special stratagem ("protein trick" (1, 2). Clinical experience has taught us the advisability of a high-protein, low-fat diet as a substitute for the primarily intended high-carbohydrate, low-fat diet. The high-protein content of this regimen compensates to a certain extent for the moderate carbohydrate ration by liberating carbohydrate from the protein at a ratio of fifty-eight per cent. It was found that the effect of dietary protein on the blood sugar was negligible and thus affected glycosuria much less than equivalent amounts of sugar given directly as carbohydrate foods (21). In addition, the high-protein, low-fat content offers certain advantages for the treatment of mild cases of diabetes so frequently associated with obesity.

It is interesting that similar considerations and short-period studies on the effect of protein foods prompted Conn and Newburgh (9) ten years later to state that there is a decided advantage to the diabetic of deriving glucose from protein. Conn (8) then recommended high-protein diets for the treatment of spontaneous hypoglycemia.

In the course of over twenty years, two forms of high-protein diets, recommended originally by Porges and myself (2), were extensively used for the treatment of mild diabetes: Diet A for obese cases and Diet B for those in approximately normal weight.

DIET A FOR THE OBESE DIABETIC

This diet consists of 100-150 grams of protein, 80-150 grams of carbohydrate and only 30-50 grams of fat. The caloric value is less than the patient's needs, e. g. 1,000 to 1,500 calories. As soon as the desired result is obtained, loss of weight and im-

20

which may have a share in maintaining the disease after it has been produced.

6. The objects of treatment therefore appears to be to destroy the saccharine process going on in the stomach, to promote a healthy assimilation, and as auxiliaries, to prevent the supposed increase of absorption from the surface, to diminish the increased action, and to change the imagined derangement of the kidneys."

The particular arrangement of the treatment as resolved upon, was as follows.

1st. The diet to consist of animal food principally, and to be thus regulated:

Breakfast.—One and a half pint of milk and half a pint of lime-water, mixed together; and bread and butter.

Noon.—Plain blood-puddings, made of blood and suet only.

Dinner.—Game, or old meats, which have been long kept; and as far as the stomach may bear, fat and rancid old meats, as pork. To eat in moderation.

Supper.—The same as breakfast.

2dly. A drachm of kali sulphuratum to be dissolved in four quarts of water which has been boiled, and to be used for daily drink.

No other article whatever, either eatable or drinkable, to be allowed, than what has been stated.

3dly.

Fig. 3. Photostatic reproduction of the first diet prescribed by John Rollo on October 16, 1796, for Captain Meredith.

provement of diabetes, as much carbohydrate is substituted for protein as the patient can stand without glycosuria and as much as 20-40 grams fat are added. One may even add protein and carbohydrate, so that the caloric value covers the consumption, from which the permanent diet results.

Essentially Diet A is a reducing regimen of a high-protein content for those diabetics whose metabolic disorder does not require immediate use of insulin. It resembles the old Banting-type of diet, except for the extremely low carbohydrate content of the latter. The high protein content prevents loss of body protein which must be avoided under all circumstances. It is easily taken, has a high satiating value and allows for variety in menu. It contains enough carbohydrate to procure its protein sparing action and to prevent ketosis. The satiating effect of carbohydrate favorably compares with iso-caloric amounts of fat. The other principles of the regimen are those of any sound reducing diet (see Ten Dietary Commandments for Weight Reduction, Table I). It is advisable to supplement this diet form with an

adequate commercial vitamin preparation containing both the fat and water soluble factors.

In previous publications the objections against a regimen of this type were extensively studied and discussed (21). They concerned especially the specific "diabetogenic" and "ketogenic" effects of protein foods. A "diabetogenic" effect of protein in diabetes was only observed after prolonged periods of preceding low-protein diet. In a similar way there exists a "diabetogenic" effect of carbohydrate after preceding low-carbohydrate diets, and even possibly a "diabetogenic" effect of fat after preceding low-fat diets. In our opinion, the innocuousness of high-protein, low-fat diets for milder forms of diabetes treated without insulin and severe diabetes treated with insulin has been proven. The results of the practical application of these diets have been very satisfactory. An example is presented in Table II. It is evident that the gradual reduction of overweight is associated with a marked improvement of the diabetes. The improved carbohydrate tolerance varies considerably with the individual. In many instances normal carbohydrate tolerance or a "cure" of diabetes may be obtained after appropriate weight reduction.

DIET B FOR THE DIABETIC WITH A NORMAL WEIGHT

The diet consists of 100-150 grams of protein, 100-150 grams of carbohydrate and 50-80 grams of fat. The total caloric content is somewhat less than normal, usually around 2,000. The proportion of protein to carbohydrate depends on the tolerance of the case. As soon as the urine has become sugar-free and the blood sugar level approximately normal, carbohydrate is gradually substituted for protein to the limit of tolerance. In a favorable course, the final diet may consist of 60-80 grams of protein, 60-80 grams of fat and 150-250 grams of carbohydrate. In contrast to Diet A, Diet B almost covers the caloric requirement. In this diet, the high protein content again serves as a substitute for the intended higher carbohydrate ration and is used because of the favorable effect of protein foods on blood and urine sugar due to the slow and gradual release of the carbohydrate from the protein. It may also be tried for moderately severe patients who, for various reasons, usually psychological, are against the use of injections. Tables III and IV present examples of the effect of Diet B.

It was previously emphasized that the beneficial effects of a low-fat regimen become apparent only after a prolonged period of observation (1, 21). It usually takes a few weeks of therapy to improve the carbohydrate tolerance of the patient, to reduce or stop the glycosuria and to lower the blood sugar levels to approximately normal. The slow mode of action of the low-fat regimen might be explained by the slow rate of reduction of the fat content of the liver and the resulting increase of its glycogen.

Many cases under our observation were permanently controlled on a regimen of this type. Among

these were some who had formerly used 20-30 units of insulin daily.

A certain disadvantage is the expense connected with the high-protein diet. It can be somewhat lowered by the use of larger amounts of fish and shellfish and low-fat cheeses. A list of high-protein, low-fat foods and a few menus of diets A and B are shown in Table V. If a patient responds to the original high-protein regimen persistently with excessive glycosuria and hyperglycemia, and if the carbohydrate tolerance remains to be less than 100 grams, then this regimen has to be discontinued and insulin therapy with the usual dietary management has to be instituted.

CONTRAINDICATIONS

The high-protein diet is contraindicated in patients with impaired kidney function and nitrogen retention. Diminished ability to concentrate and dilute (fixation of specific gravity of the urine) excludes the use of this diet regimen and necessitates the use of an average or even high-carbohydrate diet plus insulin. It must be stressed, however, that arterial hypertension per se does not represent a contraindication for the use of high-protein diets in diabetes. We have used these principles in a large group of hypertensive diabetes with obesity and could observe that a reduction of weight resulted frequently in a lowering of the blood pressure level and improvement of the symptoms of hypertension.

HIGH-PROTEIN DIETS IN INSULINIZED DIABETICS

High-protein diets may also be indicated in insulin treated diabetes. In all instances associated with hypoproteinemia and other forms of nutritional deficiency, high-protein diets are indicated. It is only natural that all objections based on the "diabetogenic" and "ketogenic" effects of protein food, discussed above, are not applicable to the insulinized diabetic. High-protein rations may be employed in the diet of the diabetic who has the nephrotic syndrome prior to the development of azotemia, e. g. in Kimmelstiel-Wilson syndrome, in sprue, in cirrhosis of the liver and in conditions associated with loss of protein and nutritional failure (severe hemorrhage, extensive burns, after operations, etc.), or requiring larger amounts

of protein for other reasons (pregnancy). Then the protein quota of the diet should be at least 100 grams and preferably more. Intravenous administration of protein hydrolyzates may be used to supplement the diet.

There is evidence that the proper utilization of Vitamin A is bound to the normal content of protein in the tissues, especially in the liver (5). Vitamin A apparently is attached to a protein component and stored in the liver as such. Similarly, normal protein balance is essential for the metabolism of at least some factors of the Vitamin B complex. Already Goldberger (12) emphasized the fact that protein of good quality (lean meats and milk) is among the best pellagra-preventive foods. Therefore, it is justified to employ high-protein diets in all instances of "nutritional decompensation," provided that other complications do not forbid their use (e. g. azotemia).

The lipotropic effect of these diets prevents the accumulation of excessive amounts of fat in the liver raises its glycogen contents and thus causes improved carbohydrate tolerance. Considerable insulin sparing effects may be accomplished in patients requiring excessively high doses of insulin and in "insulin resistant" diabetes.

SUMMARY

1. High-protein, low-fat diets have been used for the treatment of mild and moderately severe cases of diabetes requiring no (immediate) insulin therapy.
2. Patients with obesity, as well as in normal weight, have been subjected, with satisfactory results, to this form of diet treatment (diet forms A and B).
3. The high-protein content of the diet is a substitute for a higher carbohydrate ration in the non-insulinized diabetic and is better tolerated because of the slow process of liberation of the carbohydrate from the protein.
4. High-protein diets are indicated in insulin treated diabetes with sprue, liver disease, nephrotic syndrome (in the pre-azotemic stage), in all conditions associated with hypoproteinemia or other forms of nutritional failure and in "insulin resistant" individuals.

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TABLE I

Ten Dietetic Commandments for Weight Reduction

- I. Reduce caloric intake below energy requirement of patient.
 - a. 800 calories. Short individuals, sedentary occupation, moderate rate of weight reduction desired.
 - b. 1200 calories. Medium height, moderately active occupation, moderate rate of weight reduction desired.
 - c. 1500 calories. Tall individuals, manual occupations, slow rate of weight reduction indicated by medical condition, inability of patient to adhere to lower caloric diets due to untoward symptoms, social or other reasons.
- II. Allow adequate protein intake. Greater proportion of protein necessary. 100 to 150 grams or more.
 - a. Prevents negative nitrogen balance.
 - b. Creates higher specific dynamic action.
 - c. High satiating value.
 - d. Allows for variety in menu and is easily taken.
- III. Permit adequate carbohydrate intake. At least 80 to 100 grams.
 - a. Protein sparing action. Helps prevent protein deficiency.
 - b. Antiketogenic action. Essential in preventing acidosis.
 - c. Satiating effect greater than fats. Less than proteins.
 - d. Satisfies usual dietetic habits and gratifies desires.
- IV. Limit fat intake. Not more than 50 grams.
 - a. Highest caloric value. Nine calories per gram.
 - b. Easiest to eliminate, both from gustatory and nutritional viewpoints.
 - c. To eliminate the possibility of acidosis.
- V. Give adequate vitamin intake.
 - Vitamin A. Milk, butter, green vegetables, carrots.
 - Vitamin B. Cereal, yeast, most fruits, vegetables, lean meats.
 - Vitamin C. Fresh fruits, vegetables, liver.
 - Vitamin D. Green leafy vegetables, egg yolk.
- VI. Give adequate mineral intake.
 - a. Calcium. Milk, pot and farmer cheese, turnips.
 - b. Phosphorus. Cheese, egg yolk, beans, grain.
 - c. Iron. Blood, beef juice, parsley, lima beans.
 - d. Copper. Calve's liver, cocoa, oysters, beef.
 - e. Iodine. Sea food, salmon, tuna fish, green peas.
- VII. Regulate fluid-salt allowance when necessary.

Unlimited fluids and salt permitted except where manifest water retention occurs.
- VIII. Give adequate bulk.

Necessary to fill the stomach and stimulate intestinal motility and secretion.
- IX. Satisfy personal preferences.

As far as possible within dietary limitations.
- X. Vary menus and foods.

In order to provide a well-balanced menu and psychological satisfaction.

TABLE II

Date	Glycosuria gms.	Blood sugar mgs. %	Body weight lbs.	Diet COH	Diet P	Diet F
1/6-1/13	8.4-20.5	228	167	70	70	130
1/14-2/3	0-7	207	163	110	120	40
2/4-3/8	0	128	160	110	105	60

Mild case of diabetes and obesity, treated with a high protein, low fat diet, shows a loss of six pounds of body weight and marked improvement of diabetes.

TABLE III

Date	Glycosuria gms.	Blood sugar mgs. %	Body weight lbs.	Diet COH	Diet P	Diet F
3/9-3/14	13.9-25.0	218	165	70	70	130
3/15-3/23	5.-21.0	205	164	130	140	70
3/24-3/28	0	175	161.5	120	140	70
3/29-4/5	0	131	165.25	130	140	70

Mild case of diabetes in normal weight. Type B diet results in subsidence of glycosuria and lowering of blood sugar while weight remains unchanged.

TABLE IV

Date	Glycosuria gms.	Blood sugar mgs. %	Body weight lbs.	Diet COH	Diet P	Diet F
11/15-11/22	15.6-18	164	168	80	80	130
11/22-12/9	0	118	166.5	130	160	70
12/9-1/3	0	162	167	130	160	70
1/3-1/16	0	169	170	120	70	70
1/16-1/23	0	124	167.5	170	120	70
1/23-2/21	0	116	167.5	200	90	70

Mild case of diabetes in normal weight, treated with Type B diet. After the blood sugar levels and urine became sugar-free, the protein content was gradually reduced from 160 to 90 grams with concomitant elevation of the carbohydrate from 130 to 200 grams.

TABLE V*

List of Foods Low in fat and High in Protein

Lean meat: Lean pieces of beef, mutton, veal, beef tongue, game (venison, hare), breast of lean young chickens, pheasants, pigeons, partridge, wild duck, sweetbreads. Visible fat should be removed.

Fish: Pike, haddock, cod, river perch, sole, red snapper, halibut, sea-pike, trout, salmon trout, tench, pike-perch, lobster (without fat), crab meat, mussels, oysters, sardines.

Cheese (lean cheese): Pot cheese or curds, Swiss cheese (lean) and occasionally medium-fat such as parmesan.

Buttermilk.

Egg-white. Powdered skimmed milk.

Gelatine, aspic, meat jelly, protein preparations like amnolds, amigen, etc.

Meat broth (skimmed).

Directions for High-protein Diet

This diet presents no difficulties when large amounts of meat, fish and fowl may be taken. When this is not the case, other high-protein foods must be largely substituted and used according to the patient's need.

* The following diets are partially based on previous work and publications by Porges and myself (21).

1. Lean Cheese.

Lean cheese (pot or cottage, curds, etc.), may be given in certain quantities with bread. One may also stir up cottage cheese, curds, possibly also parmesan cheese in soups, sprinkle over or mix with vegetables; cheese sticks, cheese cake and curd cake may be prepared with limited amounts of fat, egg-white and flour.

2. Gelatine, Aspic, Meat jelly

3. Egg-white

Egg-white may be used in soups, with vegetables, etc., with salad, meat, fish, potatoes and vegetables. It may also be used with flour in the form of omelettes and similar dishes.

4. Prepared Protein Foods

These may be given with soups, vegetables, fruit or vegetable juices.

Diet Models for High-protein, Low-fat Diets

1. Diet Model for calories 1200, carbohydrate 80, protein 120, fat 40 gms:

Breakfast

	COH gms.	P. gms.	F. gms.
2 eggs		12	10
1 slice bread	12	2	
1 oz. pot cheese	1	6	
Coffee			
	13	20	10

Lunch

4 oz. pot cheese	4	24	
1 3% vegetable	3	1	
1 slice bread	12	2	
1 2% fruit	9	1	
8 oz. skimmed milk	12	7	
	40	35	

Supper

6 oz. meat or fish		48	33
1 3% vegetable	3	1	
1 slice of bread	12	2	
1 oz. pot cheese	1	6	
8 oz. skimmed milk	12	7	
	28	64	33
	81	119	43

2. Diet model for calories 1540, carbohydrate 100, protein 150, fat 60 gms.

Breakfast

1 12% fruit	12	1	
2 eggs		12	10
1 slice bread	12	2	
1 tsp. butter			4
1 oz. pot cheese	1	6	
	25	21	14

Lunch

6 oz. pot cheese	6	36	
1 3% vegetable	3	1	
1 slice bread	12	2	
1 tsp. butter			4
1 6% fruit	6	1	
8 oz. skimmed milk	12	7	
	39	47	4

Supper				Lunch			
	COH gms.	P. gms.	F. gms.		COH gms.	P. gms.	F. gms.
8 oz. meat or fish		64	44	5 oz. meat or fish		40	30
1 6% vegetable	6	1		1 9% vegetable	9	2	
1 slice bread	12	2		1 slice bread	12	2	
1 oz. pot cheese	1	6		1 oz. pot cheese	1	6	
1 6% fruit	6	1		1 tsp. butter			4
8 oz. skimmed milk	12	7		8 oz. skimmed milk	12	7	
	37	81	44	1 12% fruit	12	1	
	—	—	—		46	56	34
Total	101	149	62				
2. Diet model for calories 1800, carbohydrate 120, protein 150, fat 80 gms:				Supper			
Breakfast				6 oz. meat or fish		48	33
1 12% fruit	12	1		1 18% vegetable	18	3	
2 eggs		12	10	1 6% vegetable	6	1	
1 slice bread	12	2		1 slice bread	12	2	
1 tsp. butter			4	2 oz. pot cheese	2	12	
1 oz. pot cheese	1	6		8 oz. skimmed milk	12	7	
Coffee	—	—	—		50	73	33
	25	21	14		—	—	—
				Total	121	152	81

Malnutrition and Vitamin Deficiency in Recently Released Prisoners of War

By

A. ALLEN GOLDBLOOM, M.D., F.A.C.P.

ABRAHAM LIEBERSON, M.D.

NEW YORK, N. Y.

and

CHARLES D. ROSEN, M.D.

EAST ORANGE, N. J.

WITH MALNUTRITION the most widespread disease in the post-war world any investigation on a large scale of this subject becomes of interest to all physicians (1, 2, 3, 4, 5). At Camp Kilmer, N. J., we had the opportunity in the summer of 1945 to examine carefully a group of 121 prisoners of war who had been released from 18 different German prisoners of war camps from 18 to 22 days before (average was 21 days). They had been put on high caloric, high vitamin diets immediately upon release and returned to the United States for further treatment preparatory to discharge. The exact rations received daily by each prisoner of war was noted and its nutritive value calculated (Table I). A perusal of this table shows how hopelessly inadequate the diets were, especially when compared with the minimum daily requirements suggested by the National Research Council. We thus see that the average ration of the 18 camps supplied only 12% of the cal-

ories needed, some camps furnishing as little as 128 calories a day, while the maximum supplied was 684 calories. The proteins furnished varied from 4 to 22.4 grams a day, and averaged 8.4 grams or only 12% of the recommended daily allowance of 70 grams. The fats, supplied at different camps showed the greatest variations. At some camps as little as .5 gram was rationed out, while at the best camps 25 grams was supplied. (The average was 3.8 grams of fat a day, less than 7% of normal). The carbohydrates furnished showed much less variation — from 25.7 to 110.4 grams a day. The average was 48.6 grams or about 13% of the amount usually recommended.

The mineral content of the rations furnished at various camps also showed marked variations. The Calcium varied from .014 to .148 gm. per day, with an average of .040 gm. (only 5% of the .8 gm. recommended). The phosphorus varied from .067 gm. to .283 gm. with an average of .162 gm. Although the phosphorus needs of the body have not been agreed upon yet, the average figure quoted is about 2 gm. This would mean that the average camp ration of

From the Medical Service, Station Hospital, Camp Kilmer, New Jersey.

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phosphorus was only 8% of the recommended amount. There was less variation in the iron content of the prison diets, the lowest being .9 mg. and the highest 4.3 mg. with an average of 1.9 mg. or about 16% of the daily recommended allowance of 12 mg.

In the vitamin category the greatest variations were found in the Vitamin A contents. These varied from a low of 31 I. U. to a high of 994 I. U. The average Vit. A content was 214 I. U. or about 4% of the daily requirements (5,000 I. U.). There was less variation in the amounts of thiamin chloride furnished. This varied from 114 to 621 micrograms with an average of 263 micrograms, or 18% of the daily requirement (1500 micrograms). The rations were more deficient in riboflavin however. From 52 to 280 micrograms were furnished at the different camps, the average (127 micrograms) being only 6% of the daily requirement (2200 micrograms). The niacin content was only a little better in most camps. It varied from .85 to 4.81 mg. with an average of 1.44 mg. (about 10% of the recommended 15 mg. per day). The content of vitamin C in the prison rations was better than the other vitamins (probably because of the prominence of potatoes in the diet). It varied from 4.5 to 41 mg. with 18.6 as the average. This is about 25% of the recommended daily allowance of 75 mg.

The average stay of these 121 prisoners in the detention camps was 231 days (varied from 8 to 820 days) and the average weight lost in camp was 29.3 lbs. (varied from 0 to 60 lbs.). Considering that the rations furnished on the average only 10 to 20% of the dietary needs we would expect that examination only three weeks after liberation from prison camps would show marked signs of malnutrition and vitamin deficiency. On the contrary, examination showed little evidence of clinical or vitamin deficiency. Apparently in the short three weeks access to full diets, the average prisoner had gained back 13.4 of the 29.3 lbs. weight lost in camp. Only one prisoner showed moderate signs (+ +) of vitamin deficiency (painful calves, tingling toes, roughened skin and painful tongue). In all the other cases the signs of vitamin deficiency when found were of minimal degree (+). This astounding fact is graphically illustrated in Fig. I. which shows the relative frequency of the various vitamin deficiencies encountered in these men. When we consider that a one-plus polyvitamin deficiency is often found in our "well-fed" civilian population, the relative freedom from vitamin deficiency that these prisoners of war showed three weeks after liberation becomes more significant yet. There are several factors which help explain the relatively good nourishment of these prisoners of war. There is no doubt that in a great many cases the rations were supplemented adequately by legal means, such as the Red Cross Food Packages, and again by bribing of prison guards, etc. The average delivery of Red Cross packages in the camps studied was a package in two weeks, although this varied from no parcels to three parcels in two weeks.

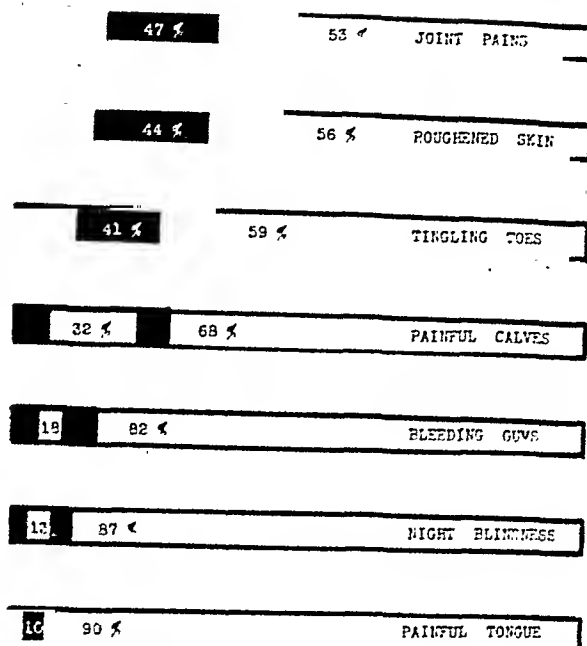


Fig. I. Relative Frequency of Signs of Various Vitamin Deficiencies in 120 Prisoners of War Three Weeks After Liberation From 18 Different German Prisoner of War Camps.

Black — Minimal (+) Clinical Evidence of Vitamin Deficiency.

Blank — No Clinical Evidence of Vitamin Deficiency.

Even when the parcels were received only irregularly their highly concentrated nutritional value added considerably to the nourishment obtained from the regular camp ration and is probably the most important single factor in the survival of these prisoners. Table II is an analysis of the Standard Package (number 10) sent to the camps. This demonstrates the highly concentrated food value of the package and indicates that if it were received every week, the recommended allowance per day, per man could be met almost completely. A factor which must be mentioned is the barter value of the cigarettes and soap furnished by the parcels, for they were very high in the black market bartering that sprang up in most of the camps. Those prisoners who had a well organized barter system in camp and shared their parcels equitably showed the least undernourishment. Those who worked on farms and were able to supplement their diets by the increased rations picked up on the farm also showed only slight evidence of nutritional failure.

There were also certain physiological factors that tended to compensate for the reduced rations. A more detailed study of the weight lost by these prisoners in camp illustrates clearly one of these mechanisms of adjustment. The average weight loss per prisoner was 29.3 lbs. varying from 0 to 65 lbs., depending on the length of imprisonment and the particular camp the prisoner had been in. The average weight loss for those who had been in camp for 30 days or less was 1.31 lbs. per day. In contrast to this, the average for those who were in camp 60 days or less was

TABLE I
A DIETARY SURVEY OF THE RATIONS FURNISHED
AT 18 GERMAN PRISONER OF WAR CAMPS
(AVERAGE PER CAPITA PER DAY)

Camps	Rations Furnished	VITAMINS											
		Cal.	Pro. Gm.	Fat Gm.	CHO Gm.	Ca Gm.	P Gm.	Fe mg.	A I. U.	Thiamine mcg.	Riboflavin mcg.	Niacin mg.	Ascorbic Acid mg.
No 1	1 slice black bread, 3 boiled potatoes, 1 cup dehydrated vegetable soup, 1 tablespoon barley.	452	14.4	2.2	64.0	.076	.283	3.5	541	487	182	3.06	41
2	1 slice black bread, 3 potatoes, 1 cup thin soup.	363	10.3	1.3	48.0	.047	.208	2.4	321	366	142	2.07	37.5
3	2 slices black bread, 3 potatoes, 1 cup thin soup, 2 oz. sausage.	684	22.4	25.0	62.9	.059	.367	4.3	341	621	280	4.81	37.5
4	1 slice black bread, 1 cup thin soup, 1 cup coffee, 1 tspn. sugar.	223	4.4	11.5	25.7	.028	.069	.9	468	115	63	.92	4.5
5	1 slice black bread, 4 boiled potatoes, 1 cup potato soup.	496	12.0	.9	110.4	.042	.280	3.0	185	510	188	2.65	55
6	1 slice black bread, 3 potatoes, 1 cup dehydrated grass.	346	9.1	1.0	50.1	.037	.197	2.2	111	348	131	1.91	33.2
7	1 cup potato soup, 3 crackers, 1 level tspn. jelly.	263	4.4	3.1	54.3	.016	.109	1.2	39	167	74	.93	11
8	2 slices black bread, 3 potatoes, 1 cup soup, 1 cup coffee.	472	14.6	2.4	68.7	.072	.276	3.3	531	480	206	3.00	42
9	1 cup cereal, 1/2 oz. powdered egg, 1 cup cocoa, 2 crackers, 1 tablespoon jelly.	474	15.6	13.2	73.6	.148	.269	3.6	994	250	351	1.31	trace
10, 11	1 slice black bread, 1 cup potato soup.	156	4.	.5	34.0	.014	.092	1.0	37	150	52	.85	11
12, 13 14	Two slices black bread, 1 cup potato soup.	227	6.	.9	48.9	.021	.137	1.5	43	210	70	1.25	11
15, 16 17, 18	1 slice black bread, 1 cup thin soup, 1 tspn. sugar, 1 cup coffee.	128	4.3	1.0	25.7	.026	.067	.9	31	114	63	.92	4.5
	Total	5277	150.4	68.1	875.2	.722	2.921	34.5	3858	4730	2183	25.99	334.7
	Average	293	8.4	8.4	48.6	.040	.162	1.9	214	263	127	1.44	18.6
Recommended Daily Allowance for 70 Kg. Man (Sedentary)		2500	70	(50-70)	(350-400)	3.	2.	12.	5000	1500	2200	15	75
% of Recommended Diet Furnished by Ration		12%	12%	7%	12%	5%	8%	16%	4%	18%	6%	10%	25%

.45 lbs per day; for 90 days or less the weight loss was .34 lbs. per day; for 120 days or less .26 lbs. per day, and for 180 days or less .19 lbs per day. The human body thus shows a definite adjustment to weight loss protecting it after the heavy loss initially. Adaptation to some deficiencies appears to be achieved if the difficulty is not too acutely precipitated. This finding agrees closely with the work of Youman and Associates (6). The reduced weight of the prisoner further reduces his mass and the daily caloric requirement. Those prisoners who were not forced to work hard or go on prolonged marches

made unusually good adjustments in this manner by reduction in body size, basal metabolism and metabolic needs. On the other hand those who were forced into hard labor did not in general survive the undernourishment, and thus do not form the subject of this report.

SUMMARY AND CONCLUSIONS

The remarkable recuperative power of the human body after prolonged periods of marked systematized undernourishment is illustrated by careful physical examination of 121 American soldiers released

The Etiologic Diagnosis of Ulcerative Colitis

By

WILLIAM Z. FRADKIN, A.B., M.D.

BROOKLYN, N. Y.

THE ETIOLOGIC DIAGNOSIS of Ulcerative Colitis is the responsibility of the Gastroenterologist. It is he who is called for counsel or treatment of this most devastating disease syndrome. In order to establish a complete and accurate diagnosis, it is extremely important that the Gastroenterologist formulate and follow a definite clinical and laboratory plan.

Clinically, the ulcerative disease can be identified by a detailed chronologic history, a thorough physical examination, sigmoidoscopy and roentgen-ray studies. For confirmation or detection of the causative agent or agents, certain specific laboratory procedures must be instituted.

The history deals with a comparatively young adult whose complaints are those of progressive weakness, bloody diarrhea, tenesmus, poor control of bowel evacuations, loss of appetite, rapid loss of weight, intermittent fever, abdominal pains, severe anemia and nervous irritability. The symptoms of every system in the body, as well as the daily dietary and social routine, past and present, from time of arising to bedtime, must be elicited. A detailed history is time-consuming, but within the province of the specialist. It may hold the key to valuable diagnostic data.

The physical examination must not be confined to the abdomen. Suggestive diagnostic signs may be found in the skin or on examination of the head, neck, chest and extremities. The rectal examination should include inspection of the anal region and internal digital palpation. Inspection of the rectosigmoidal mucosa is not advisable at the first meeting with the patient. Not only is proper preparation of the colon required but a technical preparation for the purpose of etiologic study is the primary interest at this time. Systematically done the physical examination consumes little time in comparison to the vast amount of information acquired.

Sigmoidoscopy will usually reveal pathologic changes in the mucosa. Occasionally, however, the ulcerative process is beyond the reach of the sigmoidoscope and one must not be lulled into a sense of security prematurely by negative findings. Roentgen-ray studies may be necessary to locate the ulcerative pro-

cess in the upper colon. Inspection of the mucous membrane of the rectum and sigmoid may reveal a variety of inflammatory lesions. One may note a congested, edematous, easily bleeding mucosa, or a comparatively normal lining on gross appearance, or only nests of petechial hemorrhages here and there. Ulcerations varying in size, depth and outline covered by blood-tinged mucus are common findings in the more advanced stages. Resolution or healing of these lesions may be evident by the presence of scar tissue in the form of healed ulcer beds, or small pedunculated polypoid masses of mucosa, or narrowing of the lumen with stricture formation or chords of fibrous tissue bridges over the previously undermined mucosa.

Roentgenologically, one is impressed by the uniformity of the findings in most of the ulcerative colitis cases. The bowel fills rapidly with practically half the normal amount of barium, showing its reduced capacity, narrowed lumen and contracted and shortened structure. Ulcerated lesions are revealed by the fringed or saw-toothed outline of the barium column. The contrast air study may reveal further pathology by the moth-eaten or lace network configuration of the barium as a result of pseudopolypoid changes in the mucosa. This is obviously a late manifestation. Occasionally one encounters a mild form of the disease in which the ulcerative process is localized to the rectum, and with very little if any abnormal roentgen findings. A diagnostic opinion must therefore not be formed hastily. It should rest upon a scientific interpretation and evaluation of all diagnostic data. A small bowel study may be indicated. An X-ray examination of the chest may also be advisable.

The laboratory approach consists of a careful study of the blood for the presence of eosinophilia, a blood dyscrasia, or malarial parasites. A blood chemistry is of limited value except for ascertaining the content of urea nitrogen. The determination of ascorbic acid levels and prothrombin time may be prompted by the history and physical examination. Complement fixation tests for syphilis and amebiasis are procedures of recognized value. Blood dysentery agglutination tests are useful in the etiologic diagnosis of ulcerative colitis, only when properly controlled and the results are carefully interpreted. It is essential to study the level of the environmental normal titers with the various prevalent pathogenic strains before special diagnostic significance can be attached to *Shigella* and *Salmonella* agglutinations. The Frei test with its serum and intradermal neutralization tests, or

From the Colitis Division, Department of Gastroenterology, and the Colitis Division, Department of Laboratories, Jewish Hospital of Brooklyn.

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Submitted October 3, 1947.

TABLE II

ANALYSIS OF STANDARD PACKAGE NO. 10 FOR
PRISONERS OF WAR

	Wt.	Calories	Pro. Gms.	Fats Gms.	CHO Gms.	Ca Gms.	P Gms.	Fe Mg.	A. I. U.	VITAMINS			
										Thiamine mcg.	Riboflavin mcg.	Niacin mg.	Ascorbic Acid mg.
Milk whole powdered	16 oz.	2249	117.1	121.2	172.5	4.373	3.282	7.8	6401	1407	7219	3.0	32
Cheese, processed American	12 oz.	1338	81.6	109.9	5.8	2.973	2.076	3.3	5106	153	1872	.7	—
Army spread (butter)	16 oz.	3327	2.7	367.7	1.8	.073	.073	.9	13620		45	.5	—
Smithfield ham	12 oz.	1123	50.1	102.2	1.0	.057	.537	7.5		1941	612	9.9	—
Beef, corned	12 oz.	888	65.7	69.2	1.0	.120	.516	27.6		386	908	20.4	—
Sausage, Cervelat	6 oz.	648	37.2	55.3	—	.021	.402	5.9		340	357	4.8	—
Liver Pate	6 oz.	228	33.6	5.9	10.2	.019	.636	14.0	16025	648	5106	31.8	54
Salmon	8 oz.	375	45.9	21.3		.150	.642	2.9	635	45	363	17.4	—
Prunes	16 oz.	1154	9.1	2.3	274.2	.222	.327	10.9	7718	318	363	5.9	23
Orange Concentrate	4 oz.	300	5.4	1.2	67.2	.144	.108	2.4	1500	480	180	1.3	282
Biscuits, Type K-2	7 oz.	558	15.0	15.6	89.4	.126	.192	3.6	174	534	462	4.0	—
Chocolate Candy Bar	4 oz.	647	6.2	60.0	20.4	.102	.516	3.1	—	74	272	1.1	—
Sugar, lump	8 oz.	903			225.8								
Coffee, soluble	4 oz.									1021	80	9.9	—
Soap, 2 bars hard white	4 oz.												
Cigarettes, 80	3 oz.												
Total	138 oz.	13738	469.6	931.8	869.3	8.320	9.307	89.4	51179	7347	17839	110.7	391
Daily food value per day													
If Pkg. rec'd every 2 weeks.		981	33.5	66.5	62.1	.594	.664	6.4	3655	525	1274	7.9	29
If Pkg. rec'd every week		1962	67.1	133.1	124.2	1.189	1.329	12.8	7311	1049	2548	15.8	57
Recommended allowance per man day		2500	70	(50-70)	(400)	.800	2.	12.	5000	1500	2200	15.	75

three weeks previously from 18 different prisoner of war camps in Germany. Only one of these prisoners showed moderate undernourishment and vitamin deficiency. More than 53% showed no evidence of any vitamin deficiency clinically, and the others

showed minimal evidence (one-plus) of vitamin deficiencies to varying extents. Analysis shows that the supplementary rations furnished in the Red Cross Packages were the most important single factor in preventing serious nutritional failure in these prisoners of war.

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cess in the upper colon. Inspection of the mucous membrane of the rectum and sigmoid may reveal a variety of inflammatory lesions. One may note a congested, edematous, easily bleeding mucosa, or a comparatively normal lining on gross appearance, or only nests of petechial hemorrhages here and there. Ulcerations varying in size, depth and outline covered by blood-tinged mucus are common findings in the more advanced stages. Resolution or healing of these lesions may be evident by the presence of scar tissue in the form of healed ulcer beds, or small pedunculated polypoid masses of mucosa, or narrowing of the lumen with stricture formation or chords of fibrous tissue bridges over the previously undermined mucosa.

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the isolation of the virus from the rectal tissue will unquestionably establish the presence of infection with the virus of lymphogranuloma venereum in the occasional case of ulcerative colitis.

Finally, and of immense diagnostic importance, is the routine practice of repeated microscopic and cultural examinations of aspirated material obtained directly from the ulcerative lesions through the proctosigmoidoscope. The sigmoidoscopic aspirator, devised by the author in 1933, has been used to obtain such material. It aspirates exudate from the depths of ulcers and the crypts of the mucous membrane thus furnishing ideal material which is most likely to reveal the causative organism. Specimens must not be aspirated following soapsuds enemas, or while bacteriostatic drugs are being used. The procedure should obviously be avoided for at least 72 hours following the use of barium for X-ray

studies. Several smears must be made routinely of the aspirated specimen for study with Gram, acid-fast, and iron hematoxylin stains.

The rectosigmoid aspirator has also been used for the aspiration and collection of fresh rectosigmoidal material with excellent results. This instrument makes possible the collection of a stool suspension through a sterile field and into a sterile test tube. It eliminates the irritation of repeated sigmoidoscopies and simplifies the handling and transportation of the fresh specimen. It also avoids outside contamination from bedpans, paper and glass containers.

To summarize — the mere diagnosis of Ulcerative Colitis or "Idiopathic Ulcerative Colitis," or "Nonspecific Ulcerative Colitis," is incomplete, of limited prognostic or therapeutic usefulness, and often leads unnecessarily to long periods of invalidism. An etiologic diagnosis must be the objective of the Gastroenterologist.

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Treatment of Diarrhoea

By

ALFRED J. CANTOR, M.D.

FLUSHING, N. Y.

REGARDLESS OF the etiology of a particular diarrhoea certain general principles have been established for treatment. We shall here discuss these general principles. In addition to the general therapy outlined, specific treatment for the particular diarrhoea should be employed as soon as a diagnosis is made. In the interim before diagnosis, and during the specific period of treatment as well, the general measures to be described are employed.

These general measures are supportive in most cases. Frequently they will make the difference between a successful outcome and a loss of life. The very great loss of water, proteins, salt and vitamins during an active diarrhoea may be a threat to life.

The loss of fluids is often so great that an extensive dehydration develops. Associated with this de-

hydration is a loss of chlorides and a concentration of the blood stream. The blood urea rises and the blood chlorides fall. The clinical appearance of the patient suffering from dehydration is well known. The skin becomes dry and loses its flexibility. The tongue is dry. The patient actually looks dried out and the eyes are often sunken.

In these cases *intravenous therapy* must be employed at once. Five per cent glucose in saline is given intravenously until there is clinical improvement. The glucose provides caloric intake, and the blood chlorides are improved by the saline. Two thousand to three thousand cc. of this solution may be required daily. It is best to alternate continuous infusions of this nature between the veins of the arm and those of the leg, for the therapy must often be continued over a period of days.

Hypoproteinemia rapidly develops in many patients. Protein deficiency results from the excretion of protein from an over-active intestinal tract. Hypermotility of the intestinal tract and the loss of glandular secretions prevents adequate digestion and absorption of proteins.

Once again the clinical picture is evident. The patient is very weak from loss of nutrition. Hypoproteinemia is further evidenced by a pitting oedema of the ankles and a puffing about the eyes. Clinical examination demonstrates a low blood pressure, rapid pulse and a severe anemia. The blood chemistry reveals an inversion of the albumin-globulin ratio and a low serum protein.

It is interesting to note that the oedema produced by the hypoproteinemia is to be found in the intestinal tract as well as in the ankles and eye-lids. The gastro-intestinal mucosa is oedematous, and this further prevents adequate digestion and absorption.

Again we must rely upon intravenous therapy. Anigen, an enzymatic hydrolysis product of casein, is particularly valuable. To restore blood volume and plasma protein level whole blood and plasma should be employed. Whole blood will rapidly restore the red blood cell volume.

Oral amino acid therapy should not be employed until the patient is clinically improved. Oral amino acids often increase the tendency to diarrhoea, and should not be employed until the gastro-intestinal tract oedema is entirely relieved.

A high protein, high caloric and low residue *diet* may be prescribed during the last stages of parenteral feeding. During the early stages of oral feeding food is added very gradually. Such foods may consist of tea, preferably green tea, rice water and barley water, ripe, brown-flecked bananas and boiled or steamed rice. If these foods are well tolerated the high caloric and high protein diet may be instituted. All food must be appetizing to the patient. Additions must be made gradually. It is best to avoid fruits, fruit juices and vegetables during the early stages. When the patient shows sufficient improvement to tolerate these they should be added. Meanwhile, the hypovitaminosis of diarrhoea is treated by intramuscular or intravenous therapy. An excellent preparation is Solu-B. Large doses of ascorbic acid, riboflavin and niacinamide, as well as thiamin chloride, should be given by the parenteral route.

Vitamin A may be given orally in capsules. A single capsule of 5,000 to 10,000 U. S. P. units should be given. Thiamin chloride should be given in large dosage; approximately 100 mg. parenterally. Riboflavin and niacinamide may be given in the form of Solu-B, which contains 10 mg. of riboflavin and 250 mg. of niacinamide in 5 cc. of distilled water. It is best to give between 15 and 25 mg. riboflavin, 150 to 500 mg. of niacinamide and 10 to 100 mg. of thiamin chloride daily.

Ascorbic acid will be required in a dosage of 150 to 1,000 mg. daily, and may be given parenterally in 2 cc. ampoules of 100 mg. each. Vitamin D is recommended in a dosage of between 500 and 1500 U. S. P. units daily. Vitamin K is employed only if there is a prolonged prothrombin time. A parenteral dosage of 5 or 10 mg. will be required.

In addition to these preparations liver extract should be recommended intramuscularly, at least three times a week. After the first week or two, depending upon the degree of clinical improvement, it may be possible to give these vitamin preparations orally. When this occurs the dosage will be reduced and a maintenance dosage substituted. For Vitamin A the maintenance dosage is 5,000 to 8,000 units daily, for thiamin chloride 5 mg. daily, for riboflavin 5 mg. daily, for niacinamide 25 mg. daily, for Vitamin D 500 U. S. P. units daily, for ascorbic acid, 50 mg. daily, and for Vitamin K from 1 to 2 mg. daily. Of course the natural food sources of the vitamins will be employed exclusively as soon as the clinical condition warrants a high vitamin diet. During the early stages of dietary therapy, while fruits and fruit juices and vegetables are not desirable, supplementary vitamin preparations must be employed actively.

During the early stages of therapy, while diet is limited, it will be necessary to supplement minerals as well as vitamins. Iron must be used with caution inasmuch as it frequently aggravates diarrhoea. This is due to the fact that iron is excreted through the colon. Iron may be employed parenterally. If there is a macrocytic anemia folic acid may be given by mouth in 5 mg. tablets. The dosage will be approximately 15 mg. daily for adults. A calcium lack may be corrected by oral or intramuscular administration of calcium gluconate. Calcium ascorbate may be given daily parenterally. Each 5 cc. ampoule of this preparation supplies approximately 47 mg. of calcium and 413 mg. of ascorbic acid in 5% dextrose. It is best to avoid the oral route in administering calcium.

Do not permit milk. Broths and cocoa may be allowed and small amounts of carbonated water. Bland cereals such as Farina and Cream of Wheat are then added, followed by toast, soft boiled or poached eggs, stewed breast of chicken, and mashed baked potato.

Avoid all soups other than broths. No alcohol is permitted and no fried foods. Spices are prohibited. No pastries or candy should be allowed.

Grated raw apple, one to two tablespoons every one or two hours, is sometimes very effective in controlling diarrhoea. Apple pectin may be given, and is effectively combined with kaolin.

Any food to which there is a known intolerance should be avoided. As soon as tolerated at least eight glasses of water should be taken daily. It is best to avoid candies, jams, and jellies until very late in dietary therapy.

Supportive *drug therapy* must be employed in the general management of the diarrhoeal patient. We

have already discussed the use of vitamins and minerals. We have mentioned calcium gluconate and calcium ascorbate. Calcium gluconate will relax intestinal spasm and may be given intramuscularly or intravenously. It is preferably given intravenously, although the intramuscular route provides a more prolonged effect. When there is clinical improvement, and the patient can tolerate calcium salts orally, the lactate may be given in 5 gram dosage or the gluconate in 15 gram divided daily dosage. It must always be remembered that Vitamin D is required for adequate absorption of calcium. Between 500 to 1,500 U. S. P. units of Vitamin D should be prescribed daily.

Sedation is often required in these cases. A 3 grain capsule of sodium amytal or 5 grains of sodium bromide may be taken at bedtime. Phenobarbital may be advised in 1/4 grain dosage before each meal and at bedtime.

A combination of phenobarbital with an anti-spasmodic such as tincture of belladonna in 10 drop dosage is often advisable. Narcotics should be avoided. It should be recognized that morphine produces a colon hyper-tonicity and constipation merely because it reduces the propulsive motility of the colon. The stasis thus produced is harmful. If pain is so severe that morphine is a necessity it should be given in combination with atropine sulphate. Atropine sulphate alone may be of value in decreasing spasticity of the colon.

Kaolin and bismuth subnitrate, 5 grains of each, may be given in powder form. As much as 15 grains of each may be given every four hours. If there is much rectal irritation, and the diarrhoea has come at least partially under control, kaolin may be combined with aluminum hydroxide and mineral oil and given as a rectal instillation. It is probably best, however, to avoid the use of any local treatment during the early stages of an acute diarrhoea, other than the direct management of local complications. In the later and more controlled stages of the disease rectal in-

stillations may be employed for their soothing and adsorptive effects.

The sulfonamides should never be prescribed on a non-specific basis. When indicated by proper study the sulfonamides are of great value. However, they should be used only when a specific diagnosis has been made.

Psycho-therapy may be extremely important in many cases. Psycho-therapy will often be the prime treatment, aside from the non-specific factors above listed. Even when the patient has an organic diarrhoea it is very important to re-adjust his living habits. Regularity is the key-note of any regime. During the course of general treatment the patient must be re-educated in his habits of timing — meal time, sleeping time, working time, and play time. In so far as possible the patient must be made a realist, and must be educated to accept life as it is, and not as he would like it to be. Very often consultation with a psychiatrist is desirable. However, the proctologist must include considerable psychiatric management in his practice, and should be familiar with the general principles employed.

The patient must be taught to avoid extremes of emotion. The relationship between such emotional extremes and over-activity of the bowel must be explained.

Physiotherapy is often of value in producing colon relaxation, and relaxation of the patient as a whole. The use of frequent warm baths, and the use of short-wave therapy to the abdomen is of value. Gentle general massage is often helpful.

A regular afternoon nap, and rest before and after meals, is of great value for these patients.

In brief, the patient must be treated as an individual, and not as an isolated diseased bowel.

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The Symptomatology of Chronic Amoebiasis (Before and Following Treatment)

By

R. SANDLER

M.D. (BERLIN). D.T.M.H. (LONDON).

REHOVOTH-TEL-AVIV, PALESTINE

SO FAR, the symptomatology of chronic Amoebiasis has not met with particular interest. It is accepted almost dogmatically that this disease does not show any characteristic features. Most authors

are satisfied with the statement that the symptoms of Amoebiasis are extremely variable and may imitate any other abdominal disease, to such a degree, that the clinical condition alone is insufficient to form a basis for suspicion, let alone for diagnosis.

This situation is most unsatisfactory, as the fact

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that every other abdominal disorder may be suspected of being caused by *Endamoeba histolytica*, hardly provides the stimulus needed for the energetic laboratory search necessary to establish the presence of this parasite.

The need for establishing clinical clues becomes the more urgent, as the various physical methods of examination applicable to abdominal diseases, including X-rays, are of little help in Amoebiasis. Moreover, most cases are found in general practice outside the hospital, where X-rays are not readily available. Therefore the need for a properly taken case history can hardly be over-emphasized.

"A la fin d'un interrogatoire bien conduit, le diagnostic doit être fait," says R. A. Gutman in the beginning of his book on the clinical symptoms of abdominal disorders. Only after the history is established should any suspicion which may have arisen be confirmed by clinical and laboratory examinations. This paper intends to show that Amoebiasis is no exception to the rule, and that a thorough examination of the patient's complaints and an exact elucidation of the course of his illness can give us quite a characteristic picture, which raises at least as strong a suspicion as most of the other abdominal disorders (Craig: suggestive).

As a criterium of cure, the present statistics, based on 58 cases, rely on the clinical condition rather than on the results of stool examinations, though many of the latter were made. The clinical course was observed for a long time (averaging 13.7 months), so that not only the immediate, but also the later effects of treatment could be followed. In this respect they differ from most other investigations, which follow their patients for too short a time and therefore reach wrong conclusions. A long and exact follow up was made only by Reed and Johnstone (in 65 cases for 13.2 months on the average) and by Hakansson in 45 cases for more than a year. They, however, do not follow up the clinical course of the disease. I want to emphasize that all but four of the cases mentioned in this paper are of the chronic variety. Therefore this investigation differs widely from the exact examination of Hinman and Kampmeyer which deals only with acute cases. The details of the symptomatology of Amoebic Dysentery, as distinct from chronic Amoebiasis, are to be described elsewhere.

These 58 cases are part of 150 cases of which the symptomatology was studied. Most of them were, however, not considered in these statistics, as they have not been followed up for a sufficiently long time. All patients were diagnosed as infested with *Endamoeba histolytica* on the strength of a positive finding of the parasite in the stool, mostly after taking Magnesium Sulfuricum. The author personally supervised the diagnosis in all cases. The samples were examined in saline and Lugol's solution, part of them being confirmed by positive culture (76) and a positive Complement Fixation test (9).

All patients were industrial and agricultural work-

ers, living in a Jewish colony of 12,000 inhabitants and in a number of smaller neighboring Jewish villages. The generally accepted view that in warm countries Amoebic infection is always a grave disease and mostly appears in the form of Amoebic Dysentery is not confirmed by the author's experience. Although these cases originate from a place of subtropical character, Amoebic Dysentery is comparatively rare, at most 5%, and most patients seem to suffer from a low grade illness. The patients concerned were Jews, who, in contradiction to the negroes seen in West-Africa by Hennessey who did not exhibit any symptomatology, are sensitive and capable of explaining their subjective feelings accurately. Besides, the Jewish patients were not immune against this parasite having arrived only lately from Northern countries.

Age and Sex: 60% of our 58 cases were of the age of 20 to 40 years, which conforms with the reports of Manson-Bahr and Hankansson. The cases were divided equally among males and females in the ratio of 28:29. Canaan from Jerusalem found also almost equal numbers (196:204), nearly all Arabs, whereas Manson-Bahr and Hinman and Kampmeyer found four times as many men as women, and Ochsner even 95% men.

TABLE I

Age:	1-5	6-10	11-20	21-30	31-40	41-50	51-60	60
Nr. of pat.	2	9	5	15	22	4	2	1

ANALYSIS OF HISTORY

Duration of symptoms prior to treatment: One of the most characteristic findings is the long duration of symptoms. Table II specifies the time which passed from the beginning of the disturbances until the detection of the parasites in the stools, in 37 patients who were able to state a definite time.

TABLE II

1w	1w-4w	1-3m	4-6m	6-12m	1-2yr	2-3yr	more than 3yr
4	6	4	3	4	7	1	8

43% had already suffered for more than a year, half of them for more than three years. In view of the insidious beginning of the disease and the consequent difficulty in stating a definite time of onset, I feel that the real percentage of patients seen in the first year is still considerably smaller. Hinman and Kampmeyer saw 65% in the first year; according to Manson-Bahr, the patients present themselves on the average after five to four years, according to Reed and Al. after two years.

SUBJECTIVE SYMPTOMS

TABLE III

Subjective symptoms in adults (47 cases)

	No.	%
Gaseous distention	41	87
Diarrhea	39	83
Pains	26	55
Constipation	22	47
Dyspepsia	10	20
Tenesmus	3	5.5

Gaseous distention is the principal cause of the patient's suffering. By distention I do not mean a mere feeling of heaviness in the upper abdomen, belching or bloating, but a swelling of the whole abdomen which may cause quite severe pains and other disturbances. Like the other symptoms of Amoebiasis distention is nearly independent of such external factors, as food, exertion, nervous states etc. Its severity may vary, but it is constantly present. Food rich in cellulose may exacerbate it, but it is not abolished even by the strictest diet. I use the tolerance against oranges, which are widely eaten in Palestine, as a test for the improvement of the abdominal condition. While before treatment one slice of an orange leads to distention, after it several oranges may be tolerated without any reaction. The grade of distention is a good measure for estimating the patient's condition. According to newer opinions (Mann, Alvarez) gaseous distention may lead to disturbances of the circulation in the portal vein, to such a degree that it may interfere with liver function. This process may perhaps be held partly responsible for the bad feeling of the patient, especially after attacks of distention, and also for disturbances of the liver. Manson-Bahr finds gaseous distention as a significant symptom only in less than 10%, Hinman and Kampmeier in their dysenteric patients in 12%. Craig lays more stress on its importance.

Diarrhea and constipation: The character of diarrhetic stools in chronic Amoebiasis has been aptly described by many authors. It is, however, necessary to stress the occurrence of constipation, either alone or alternating with diarrhea. Where present, it may be quite obstinate and not less significant than the other symptoms. There can be no doubt that it is often connected with the presence of the parasite, as evidenced by the favourable influence of amoebic treatment. Six of my patients suffered from constipation alone, without ever having had diarrhea.

PAINS

TABLE IV

Localisation of Pains

	from history	On palpation
Epigastrium	13	2
Right lower quadrant	9	14
Left lower quadrant	14	16
Middle of lower abdomen	4	2
Umbilical region	1	—
Diffuse	5	—
Right upper quadrant	7	14
Left upper quadrant	3	1

Slight pains are to be found in practically every case. In a few patients they were absent altogether. Only in 55%, however, complaints on this account were stressed. As the pains are particularly caused by the abdominal distention, patients are often unable to give an exact localisation. On more accurate ques-

tioning the localisation becomes more specific. It is, however, only on palpation of the abdomen that the characteristic foci of the process, i. e. the caecum and sigmoid, are found; especially the former is often thickened conspicuously. Sometimes acute pains were felt in the region of the caecum while taking Yatren. In 14 cases there was tenderness in the liver regions, especially on fist percussion. Only in five, however, the liver was enlarged. The abdominal pains appear daily, mostly in the early morning, pass with defecation and reappear with the onset of distention. Significant tenesmi is found very seldom. Accordingly no changes were detected in the rectum where rectoscopy was done (in 17 cases). There was no connection between attacks of pains and mealtimes. Periods entirely free from pains were not met with. Four women related that during pregnancy disturbances had ceased almost entirely returning however after delivery.

Constitutional disturbances (weakness, lack of energy, apathy, nervousness, fatigue) often occur, but cannot be stated in figures. These symptoms do not seem to be affected by rest to any extent. Loss of weight was not significant. In the uncomplicated cases dyspeptic symptoms are not a part of the picture. There are no complaints of nausea, the appetite is generally good, even at the time of meteorism. Sometimes the appetite is somewhat capricious, ravenous hunger alternating with entire loss of appetite.

To sum up this chapter: A patient with a long history of continuous rather slight abdominal disturbances, consisting of gaseous distention, pains in the lower sides of the abdomen, no or only slight dyspepsia, is suspected, especially if a tender liver is found, of being infected with *Endamoeba histolytica*. It should, however, be attempted to establish the actual presence of the parasite by all available means, as only the positive finding of the parasite establishes the diagnosis.

AMOEBIASIS IN CHILDREN

The symptomatology of Amoebiasis in children is of a different nature than in adults. Instead of by permanent disturbances, the illness is characterized by short attacks between which the child feels entirely well. Out of eleven children between the ages of 2 1/2 and 11, six suffered from diarrhea, one only from constipation. Seven complained of slight pains. Four had pains without diarrhea. Only four suffered from meteorism. In two cases the liver was enlarged, but the swelling disappeared rapidly after Emetine. In two cases *Taenia saginata* gave rise to dyspeptic symptoms. The reaction to treatment (Emetine, Spiroclol, Yatren) was very prompt in five, in two older children (10, 12 years) slower. In the two infected with *Taenia* not clear. In two cases there was no improvement, probably because of familiar infection. The number of cases is actually too small to draw any conclusions. The uniform character of the symptoms which differ from those seen in adults, and the similar description given by Howell and Knott, justify the giving of the above details.

COMBINATION WITH OTHER DISEASES AND DIFFERENTIAL DIAGNOSIS

The value of a well taken history for differential diagnosis cannot be over-estimated. Unprecise ques-

tions and inaccurate answers may easily lead to a faulty diagnosis. This results not only in superfluous X-ray and other examinations, and unnecessary dietary treatment, but even in unnecessary operations. On the other hand, care should be taken not to attribute to the amoebic infection a variety of symptoms due to other diseases which may be co-existent in the same patient, like chronic gastritis, peptic ulcer, worms in the small intestine, and other protozoa. The suspicion of peptic ulcer, which was aroused erroneously in some cases, shows the need of a very strict differential diagnosis. Several patients felt alleviation of certain symptoms in the upper abdomen following the intake of meals. On closer investigation, however, it became clear that this occurrence was always merely occasional. Besides, there were never periods entirely free from abdominal disturbances. In four patients, suffering from duodenal ulcer, in addition to Amoebiasis, it was possible to distinguish easily between symptoms from the upper abdomen and those from the colon. In two cases dyspeptic symptoms might also be attributed to the finding of *Taenia saginata*, in two others to *Guardia Lamblia*. In one patient suffering from steatorrhoea the dyspeptic symptoms need not be connected at all with the amoebic infection. In a great many cases of amoebic infection pains in the upper abdomen and slight dyspeptic symptoms must be ascribed to disturbances of the liver.

A definite history of bacillary dysentery having occurred several years before was established in four cases only. Therefore it seems unlikely that bacillary dysentery plays an important part in enabling the amoeba to penetrate into the tissue through breaks of the mucosa (Acton).

LABORATORY EXAMINATIONS

As this paper is concerned with the clinical course of Amoebiasis, I wish to give only a few particulars on the results of the laboratory examinations. No significant findings were revealed in blood and urine. Gastric acidity was mostly normal, lowered only in a few cases. Systematic use of the Complement Fixation Test before and after treatment was introduced only later. Therefore figures cannot be given here. I may, however, mention that this test was of great help to us in the detection of many cases in which only few stool examinations could be made. Stool examinations were nearly always done on fresh material, after taking Magnesium sulfuricum. Therefore, free forms in motion were often found, though most of the cases were chronic. A great many control examinations were done, during and after treatment. They were continued for several months as long as clinical symptoms persisted. In several cases amoebae could be found during and immediately after treatment with Emetine. It is to be doubted whether even on the basis of several negative results during the first months after treatment, one is justified in stating that the infection has been cured. Only after a much longer time of freedom from the characteristic symptoms a cure may be assumed (S. Later).

TREATMENT

In 15 cases treatment began with a course of Emetine injections (6-8 times 0.05), followed by Yatren for a week (1.0 g. pro die) and Spirocid (Acet arson) for another week (0.5 g. pro die). After having gained the impression that Emetine does not exert any influence on the clinical symptoms of chronic Amoebiasis or, at any rate, only causes very temporary improvement, another method was tried. Only three to four injections of Emetine were given for the purpose of influencing more acute symptoms, and after this Yatren and Spirocid. Most of the patients received this course of treatment (21 with, 16 without Spirocid). After several intoxications following Spirocid had occurred in this country the use of this drug was discontinued. In later cases, which because of too short a follow up are not included in this series, Emetine was omitted altogether and only Yatren given, with or without Carbarsone. As nearly 75% of all patients did not receive Emetine or only small amounts (0.15-0.2), it can be stated that the results accomplished are due to Yatren and Spirocid. No other than the specific medication was given. No special diet was prescribed, but patients abstained from food which, according to their own experience, led to disturbances. I could not recognize any therapeutic results of dietetic measures taken before the patients received specific treatment.

Results of treatment: For the purpose of establishing the results of the therapy applied, the cases under review may be grouped under three headings:

Cured	Improved	Unchanged
29	8	21 (11+10)

This division is, however, somewhat artificial and needs explanation if the true value of the treatment is to be appreciated. The patients were followed up on the average for 13.7 months after treatment, only 11 for less than a year, but at least for 8 months. Ten were still seen after more than a year and a half, until two years. During this period they were investigated thoroughly many times, and their stools examined. As long as they continued to complain, they were seen at least every month.

Group I: Twenty-nine patients may be considered as cured, all disturbances having ceased. The most outstanding symptom, the meteorism, may serve as a sensitive test for recovery, as mentioned above. These patients were able to "forget" their abdomen and felt new strength.

Group II: Eight patients continued to suffer from gases and felt occasional pains. The stools were not regular, the general feeling was not entirely satisfactory.

Group III: Out of 21 of those who were not influenced by treatment in 11 failure must be attributed to familial infection. There remain 10 who can be said not to have been influenced at all. All these are suffering from conditions which may possibly explain

the failure. Five suffer from chronic hepatitis with an enlarged and tender liver which could not be influenced by repeated courses of Emetine. Except in one case, all the disturbances attributable to the colon also remained. Two others suffer from chronic intestinal Amoebiasis with frequent dysenteric exacerbations. There is no explanation why these seven cases complicated by hepatitis and by dysenteric reaction were not amenable to treatment. As regards hepatitis, this seems to be a rather common occurrence. One woman who did not experience any change had already suffered from steatorrhoea for 10 years. In two cases neurotic symptoms do not allow to judge the situation. One, a 56 year old man, died during a dysenteric attack complicated by peritonitis.

THE COURSE OF THE DISEASE

AFTER TREATMENT

The value of an antiamoebic drug cannot be judged according to the patient's immediate reaction. Apart from dysenteric cases, which are influenced more or less quickly, and complications outside the intestines, there is generally no significant change in the symptomatology immediately after treatment. Everything remains as before. The patient and his doctor become disappointed and try all sorts of treatment, specific and unspecific. Nevertheless, improvement slowly sets in. The patient becomes aware that lately he has begun to feel better. His stools have become more regular, the meteorism begins to decrease. It is impossible to state the beginning of this change because it sets in very gradually. I know many cases in which the change appeared only after six months and even a whole year of continued disturbances, without any further treatment having been given in the meantime. As the symptoms do not subside immediately, I think, one is not justified to speak of recurrences when exacerbations of the disturbances occur. If, after a full course of treatment, *Endamoeba histolytica* ceases to be found, one should wait patiently for improvement and not try Emetine or other antiamoebic drugs again. It must, of course, be ascertained by all means that there is no other, and especially no inalignant, disease which might contribute to the causation of the symptoms. Comparing the results of treatment in this series stated according to the disappearing of clinical symptoms, with that of Hakansson, where the results were measured according to the finding of the parasites in the stool (after Carbarsone), we find that in both 50% were influenced satisfactorily. In both the possibility of reinfection was considerable. In the series of Reed and Johnstone where the chance of reinfection was minimal, 90% were healed after treatment with Carbarsone.

SUMMARY

It is the intention of this paper to demonstrate that the clinical picture of chronic Amoebiasis is rather suggestive.

The importance of a most thorough investigation of the patient's complaints is stressed.

These statistics differ from others (a) in consisting of ambulatory cases, i. e. cases of chronic Amoebiasis without the complications mostly seen in hospitals, (b) in drawing conclusions only after a prolonged follow up.

A long history of abdominal disturbances should suffice to arouse suspicion as to their amoebic origin, especially if they are not interrupted by free periods. The most frequent and outstanding symptom is the rather grave distention, which can be used as a distinct sign for evaluating the patient's condition. Besides diarrhoea, constipation which is often favourably influenced by treatment, is a significant finding. Palpation of the abdomen gives a more specific localisation than the anamnesis. The pains do not appear in connection with the time of eating. There exist no periods entirely free of disturbances. Where the characteristic triad of symptoms — meteorism, slight pains on the sides of the lower abdomen, and especially the finding of a tender liver is found in combination with a long history of the condition, grave suspicion of an amoebic infection is justified.

Children, in contradiction to adults, suffer from short attacks. The intervals are free from symptoms.

A thorough investigation differentiates in many cases between Amoebiasis and other diseases of the abdomen, especially its upper parts. Only the positive finding of the parasite in the stool settles the diagnosis.

As Emetine has at best a temporary effect on chronic Amoebiasis. 75% of the cases were treated, in addition to a small amount of Emetine, with Yatren and Spiracid (Acetarson).

If we exclude 11 cases which because of familial reinfection were not influenced by treatment, we find that 29 out of 58 patients were apparently cured, 8 were improved and the condition of 10 did not change. In the latter cases complications, which apparently hindered improvement and healing, were always present.

Immediate cessation of symptoms after treatment is not to be expected. At best improvement will set in only after several weeks or months. After a full course of treatment improvement should therefore be awaited without resorting to a new course, as long as *Endamoeba histolytica* are not found again. The possibility of additional diseases of the bowels, especially malignant ones, should always be considered.

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Biochemical Studies of Salicylic Acid and a Series of its Derivatives

By

GUSTAV J. MARTIN, Sc.D

and

SANFORD BYERS, Ph.D.

PHILADELPHIA, PA.

ACTUTE RHEUMATIC FEVER is successfully treated by intensive salicylate therapy. Coburn (1), has outlined the therapeutic regimen which is most acceptable. It requires the maintenance of salicylate plasma levels of 35 mg. per hundred cubic centimeters. This necessitates the oral daily administration of ten gram quantities of sodium salicylate in equally divided dosages, each four hours. The logical salicylate compound for general use would be that compound which had the greatest duration of effective blood level with the least fluctuation in blood concentration.

Studies of the duration of blood levels of salicyl compounds appear to have begun with the work of Nencki (2), in 1872. He gave 4.5 grams of saligenin (salicyl alcohol) to a patient and found that it appeared in the urine as salicylic acid in ten minutes and was detectable by the iron chloride test applied to the urine for a period of 43 hours.

Hanzlik et al. (3), first reported the fact of increased destruction of salicylic acid in the rheumatic patient. The total excretion of salicyl was about 15 per cent less in rheumatic than in normal individuals. In 1919, the same laboratory (4) found that liver and other organs possessed enzymes capable of destroying salicyl and that any febrile condition increasing metabolism in general increased the degree of destruction of salicyl. In a subsequent publication (5), the duration of excretion of salicyl following a dosage from 4 to 14.8 grams of acetylsalicylic acid was reported as 4 3/4 days. Experiments in rabbits were presented by Myung (6), who reported that the concentration of salicylic acid after subcutaneous injection reached a

maximum in the blood after one hour and then diminished and disappeared in 24 hours.

Recently, Smith et al. (7), reported a series of studies on excretion duration following single doses of salicylates. Sodium salicylate in two gram doses in aviation students caused peak blood levels in two hours (15 mg.%) which diminished to around 6 mg.% in 8 hours at which time the studies were discontinued. Aspirin in similar oral doses caused peak levels at about 2 1/2 hours with a generally lower plasma level in the early phases of the study. Studies were reported by Lester et al. (8), in which acetylsalicylic acid in doses from 0.33 to 1.95 grams given to human male subjects showed variation in duration of excretion from approximately 15 to 30 hours. Depending upon the dosage, peak levels in urine were attained in from 2 1/4 to 5 hours. Plasma levels following 0.65 grams orally reached a peak in two hours at a level of about 4 mg. %. At a dosage level of 1.30 grams of acetylsalicylic acid, the peak attained was nearly 8 mg.% at about 3 hours. Lester et al. (8), from clinical observations concluded that analgesia lasted from 1 to 4 hours. These observations confirmed those of Blanchier (9), who reported excretion complete in 22 hours after 1 to 2 grams of sodium salicylate. Hanzlik et al. (10), had reported excretion of detectable amounts of salicyl for 48 hours after doses of 0.5 to 1.0 grams of various salicylates.

Method: Salicylic acid, salicylic alcohol, salicylaldehyde and acetylsalicylic acid were determined by the method of Weichselbaum (11) using Folin's alcoholic phenol reagent, and by the color reaction with ferric chloride. The determination was complicated by the fact that equimolar quantities of different compounds produce different amounts of color with either reagent, and also with the diazo reagent used by Sch-

midt (12). Hence the numerical values reported for blood or urinary aromatic hydroxy compounds would be arbitrary figures, depending upon the standard used for comparison.

In some experiments involving the feeding of mixtures of salicylic acid and saligenin, the animals were bled at hourly intervals and the blood level of phenols compared with a standard consisting of equimolar quantities of salicylic acid and saligenin. This level was reported as salicylate without any distinction between saligenin, salicylic acid or the conjugated products. It must be assumed that in any given sample salicylic alcohol, salicylaldehyde, salicylic acid and certain detoxication products will all co-exist. The ratio of color intensity given by ferric ion with salicylic acid, salicylaldehyde and saligenin is 170:40:7. By means of the ferric ion, therefore, saligenin can be prevented from contributing significantly to the assay. Salicylaldehyde will contribute, and 4 moles of salicylaldehyde will be read as 1 mole of salicylic acid.

The method of Schmidt (12) was not suited to blood level studies as it requires hours of continuous extraction for each sample and in the studies reported in this paper literally hundreds of analyses were necessary. In many individual cases, 60 analyses were required for one rabbit.

In consideration of results, it should be borne in mind that only 60-70% of ingested salicylate is recovered in non-rheumatic patients. A similar percentage value would probably apply to rabbits.

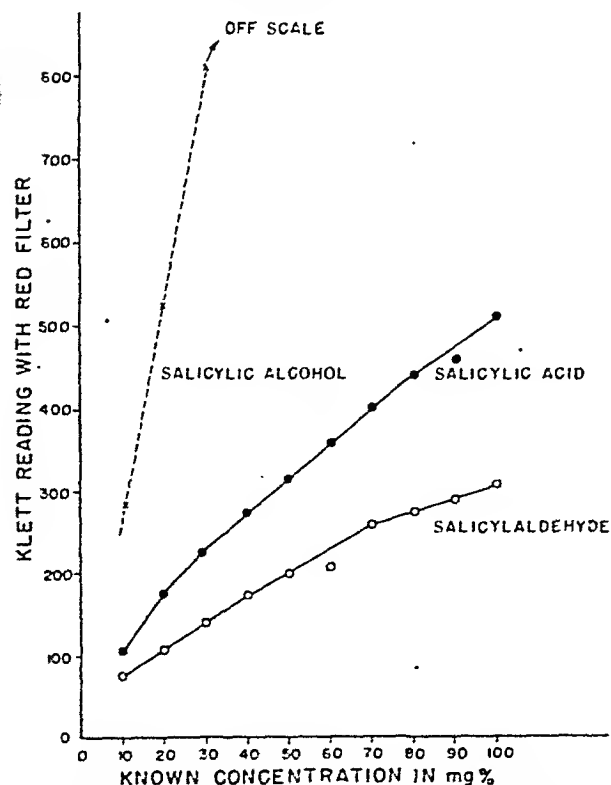


FIGURE I — Recovery of Salicylates by Folin Reagent

Mixtures of salicylic alcohol, aldehyde and acid were analyzed with the phenol reagent of Folin with the results presented in Figure 1. The color produced cannot be attributed to any single constituent of the mixture. The method was discarded as unselective. A similar situation holds true for the color produced by ferric ion. Even tests designed for recovery and differentiation of total salicylate from 48 hour urine samples are not concerned with salicyl alcohol or aldehyde recovery, and no attempt is made to assay either compound. The lengthy (3-18 hour) extractions necessary to separate various salicyl fractions in total salicylate tests also rule out the use of these methods in rate determinations. Chemical methods, such as those of Houghton and Pelly (13) (oxidation of phenol to colored indophenol by hypochlorite plus p-aminodimethylaniline) or Gibbs (14) (phenol plus quinone chloroimide \rightarrow indophenol) are also non-specific.

Thus, it is apparent that solvent fractionation with subsequent colorimetric analysis is required. To accomplish this, carbon tetrachloride, suggested by Brodie, Udenfriend and Coburn (15), used as a means of separating salicylic acid from conjugates, was used to separate the acid from the the aldehyde and alcohol. When 30 ml. of carbon tetrachloride are shaken for a short time with a fixed volume (2 ml.) of a watery or plasma solution of salicyl compounds and a drop of acid, an unknown but constant fraction (at room temperatures) of salicylic acid is removed to the organic solvent, together with all the

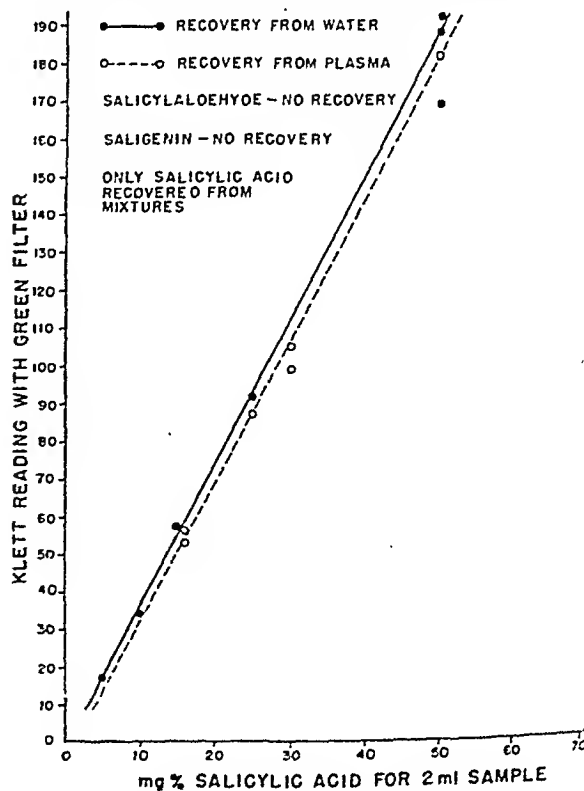


FIGURE II — Salicylate Recovery by CCl_4 , Fe^{+++} Method

salicylic alcohol and aldehyde and at least a portion of other material. If now 20 ml. of the carbon tetrachloride solution be shaken with 10 ml. of water, an unknown, but constant, fraction of the salicylic acid will enter the water layer, while all the alcohol and aldehyde remain in the CCl_4 . The watery solution of salicylic acid can then be assayed by any convenient method. A standard curve is presented in figure 2.

While normal plasma gives no color, solutions of salicylaldehyde, of saligenin, and of acetylsalicylate, give a violet color with ferric ion, but do not do so in the routine test because they are retained in the carbon tetrachloride layer. Among compounds so far tested, only salicylic acid and salicylamide give a positive test in the usual plasma analysis. Suspensions of nicotinyl salicylate (17) in water do not give a color with ferric ion. This may be because the nicotinyl salicylate is not sufficiently soluble.

Because no distinction can at present be made between salicylic acid and salicylamide, the latter compound has not been used in metabolism experiments.

Concentrations are read against the standard curve (Figure 2). It is clear that relative values are obtained. The absolute significance of the values was checked by recovery experiments and found to be within 95% of the calculated amount.

In considering data presented, it should be borne in mind that 1.35 grams of nicotinyl salicylate corresponds to 1.0 grams of acetylsalicylic acid. Therefore when 1 gram dose of acetylsalicylic acid and of nicotinyl salicylate are given to animals the blood levels for

nicotinyl salicylate should be multiplied by 1.35 for direct comparison.

RESULTS

The concentration of salicylate in rabbit plasma after injection of various levels of saligenin and salicylic acid is plotted in Figure 3. Aspirin is not sufficiently soluble for intravenous injection in quantity, so a "sodium aspirin" was injected. Aspirin is hydrolyzed to salicylate and acetate in alkali hydroxides. The degree of this hydrolysis was not determined. The final pH of the "sodium aspirin" was 6.4-6.5. The aspirin blood level curve roughly paralleled that of salicylic acid.

Saligenin-salicylic acid (neutralized) mixtures in the ratios of 1:2 and 2:1 when injected intravenously into the rabbit give rise to the appearance and elimination of plasma "salicylate" at about the same rate. This rate is, except for the first half hour, much the

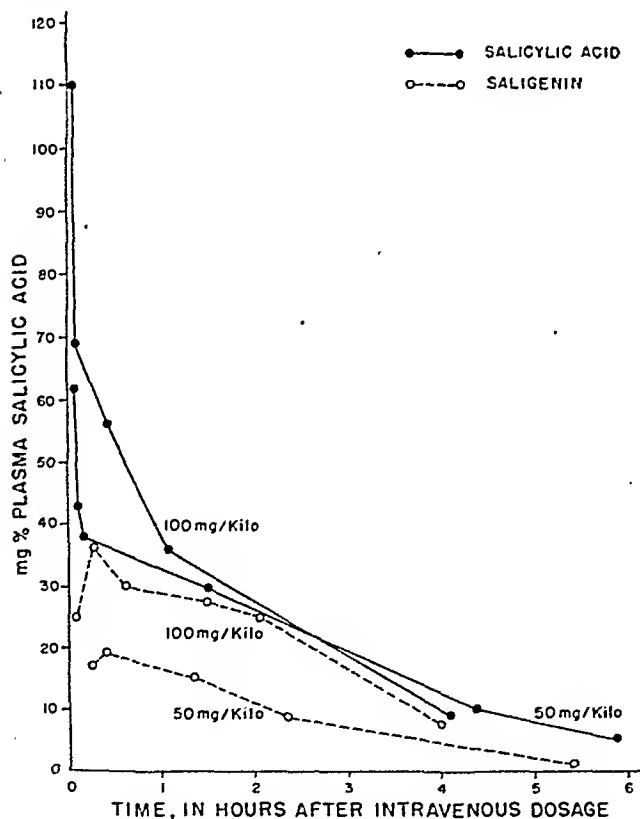


FIGURE III — Salicylate Metabolism (Rabbit)

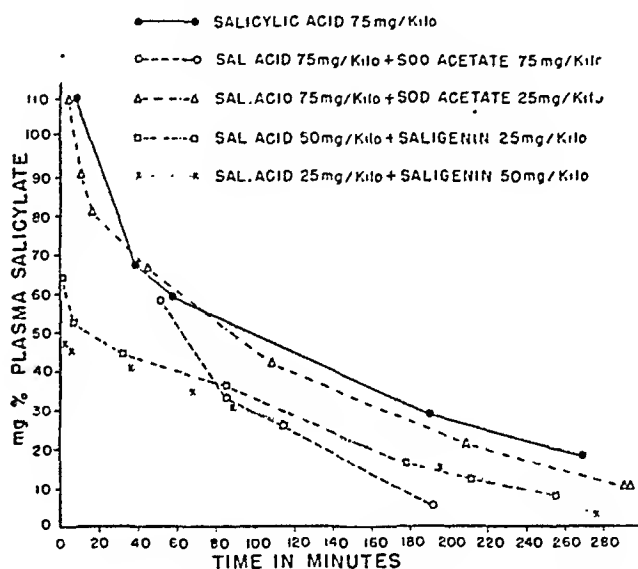


FIGURE IV — Salicylate Metabolism. Intravenous in Rabbit

same as that of the same dose per kilo of salicylic acid with or without accompanying sodium salicylate in ratios of 3:0, 3:1, and 1:1. Sodium acetate does not elevate plasma salicylate level.

Nicotinyl Salicylate. This compound, insoluble in water, was given as a suspension by stomach tube to 8 rabbits. Administered in this manner it gives rise to a somewhat delayed, but markedly prolonged appearance of plasma salicylate at a high, fairly constant level. Data are presented in Figure 5 and comparative data in Figure 6.

From Figure 6, it can be seen that a combination of 0.66 grams of nicotinyl salicylic acid and 0.33 grams of saligenin also gave a flat curve and prolonged duration.

Doses of salicylic acid: Salicylic alcohol in ratios of 2:1 and 1:2 were given to rabbits intravenously. Excretion began at once and was substantially complete after 5 hours, regardless of whether the ratio was 2:1

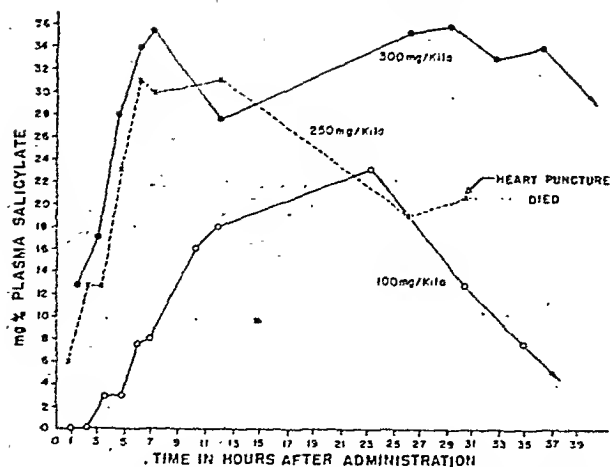


FIGURE V — Oral Nicotinyl Salicylate in the Rabbit or 1:2. Oxidation of salicylate alcohol began at once and was largely complete after 30 minutes, regardless of whether the ratio was 2:1 or 1:2.

Salicylate Metabolism. Two ml. of whole citrated rabbit blood was shaken in air with 20 mgm. of saligenin for 10 minutes. There was no detectable conversion to salicylic acid. The *in vivo* conversion of saligenin to salicylic acid, therefore, probably does not take place in the blood, but in the liver. Such a conversion by liver brei was observed.

Acetylsalicylaldehyde diacetate gives no color with the $\text{CCl}_4 - \text{FeNO}_3$ method for salicylate. It is therefore suitable for testing for *in vivo* conversion to sodium salicylate. One gram oral samples were given to each of three rabbits. Relatively low (5 mgm.%) blood "salicylate" levels resulted for 8 hours afterward. Most of the acetylsalicylaldehyde diacetate is not recoverable as salicylate.

Salicyoyl-beta-alanide was given orally in capsules to each of two rabbits in doses of 1 gram and 1.8 grams. A total of ten plasma samples was obtained from these animals at intervals for 22 hours following administration. None of these samples showed salicylate present. Salicyoyl-beta-alanide is apparently not converted to salicylate *in vivo*.

Certain other salicyl compounds were tested and found to possess little merit. Acetylsaligenin, the alcohol corresponding to acetylsalicylic acid, in a one gram dose to 4 kilogram rabbits remained in the blood stream in detectable quantities as salicyl for 2-7 hours with a period of maximum blood level between one and seven hours after dosage. The disalicylic acid ester of succinic acid showed significant blood levels for only seven hours after a one gram dose. Acetylsalicylaldehyde diacetate gave salicyl blood levels for 15 hours following a one gram dosage. These three compounds, therefore, did not give evidence meriting further study.

DISCUSSION

It is apparent from a consideration of the literature that very little work has been done on the duration

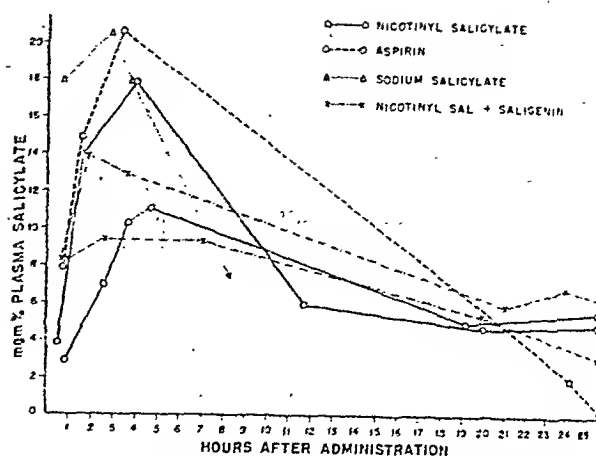


FIGURE VI — Plasma Salicylate after 1 gram Oral Dose Rabbits

of blood levels of salicyl following single doses of various salicylates and related compounds. It would seem that this is the most important aspect of the therapeutic application of these compounds. The ideal molecule would permit the attainment of relatively high blood levels of salicyl in a short period with the maintenance of that level for the greatest period. The best compound would give a blood level concentration curve without peaks; the curve would be almost flat.

Saligenin (salicyl alcohol) is oxidized rapidly and gives blood levels of salicyl following intravenous dosage roughly comparable to those of salicylic acid itself. Furthermore, the duration of significant blood levels is almost identical. This oxidation does not occur to any significant extent in the blood but is rather a function of the liver. The initial concentration of salicyl following the administration of salicylic acid is higher than that following the injection of saligenin but this difference in level has virtually disappeared by the end of the first hour. The presence of mixtures of saligenin and salicylic acid in the blood stream does not detectably alter the rate of metabolism or excretion as reflected in blood levels. Thus, the administration of mixtures of salicyl alcohol with salicylic acid or salicyl aldehyde would not seem to offer a logical approach to the problem.

Various esters of salicylic acid, however, do offer an approach to the problem. Variations in the duration of excretion of acetylsalicylic acid contrasted to that of salol are well-known. In the presently reported study, acetylsalicylic acid has been used as the standard for reference as it represents the drug of choice today.

The impossibility of predicting the structure of effective compounds for prolonged blood levels is well illustrated by two examples which were included in the present series. Salicyoyl-beta-alanide did not hydrolyze at all. It is a known displacer of pantothenic acid (16) but its structure with its simple peptide linkage would not theoretically offer any obstacle to hydrolysis and liberation of salicylate. The second

compound is acetyl salicylaldehyde diacetate. Theoretically, it should require time to hydrolyze the acetyl radicals from the molecule and in turn to oxidize the aldehyde to salicylic acid. Actually, the administration of this compound produced low levels of salicylic acid for only 8 hours.

Of the series tested which included nicotinyl salicylic acid, acetylsalicylic acid, salicylic acid, saligenin, salicyoyl-beta-alanide, acetylsaligenin, the salicylic ester of succinic acid, acetylsalicylaldehyde diacetate, and the amide of o-aminobenzoic and salicylic acids, it was found that nicotinyl salicylate gave the most prolonged blood levels with the least peaks in the curve. One hundred mg. per kilogram of nicotinyl salicylic acid given to rabbits produced blood levels which at the termination of a 40 hour period were still at 4 mgm.%. The comparable test for acetylsalicylic acid gave a picture showing complete disappearance of salicyl from the blood at the termination

of a 26 hour period. The initial level did not rise as high but remained more constant throughout the period. No basic reason can be advanced at the present time for this unusually prolonged duration of blood levels seen with nicotinyl salicylate.

SUMMARY

A series of salicylic acid derivatives was studied for duration of blood salicyl levels in the rabbit. The series comprised salicylic acid, sodium salicylate, acetylsalicylic acid, a solubilized acetylsalicylic acid, nicotinyl salicylate, salicyoyl-beta-alanide, acetylsaligenin, the salicylic acid ester of succinic acid, acetylsalicylaldehyde diacetate, the amide of o-aminobenzoic and salicylic acids, and saligenin. The effective compounds were studied in combination and singly. Of this series, the most effective single compound was found to be nicotinyl salicylate and the most effective combination was one of nicotinyl salicylate and saligenin.

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Epidemic Gastro-Enteritis

By

N. B. JAFFE, M.D.

WADSWORTH, KANSAS

THIS MALADY characterized by abdominal cramps, nausea, vomiting, and diarrhea, is more prevalent than formerly or presently recognized. Because the average case, or the majority of cases, are comparatively mild in many aspects, and because it simulates many gastrointestinal upsets, it is rarely recognized as an entity. It is variously termed as Acute Infectious Gastro-Enteritis, Intestinal Influenza, Winter Vomiting, Seasonal Gastro-Enteritis, Hanover Disease, Spencer Disease, and Devil's Diarrhea.

It is scantily described in medical literature as appearing in widespread epidemics, endemic, sporadic, and communicable disease of unknown origin. It af-

fects groups of people, schools, barracks, and isolated cases in the population. Adults are mostly affected, small children to a slight degree. It spreads rapidly, affecting many, and tapers off gradually, but seldom of long duration. The majority of cases appear in the autumn and early winter, when upper respiratory infection, and influenza prevail.

The cause is obscure, possibly a virus, affecting the nervous and digestive system. Infection of the gastro-intestinal tract, by food and drink is a possibility. Direct contact and air borne infection are also possibilities. A combination of several etiologic factors is of the most logical consideration.

The prodromal symptoms are hyperirritability, insomnia, headache, bad taste in the mouth, dyspepsia, belching borborygmus, expulsion of flatus, and general malais. The onset is generally sudden, nausea, vomiting, diarrhea, abdominal cramps, distension, tenesmus and epigastric distress. All the mentioned may be present, but at times one or two symptoms are absent. They are mostly mild, lasting twenty-four hours or a few days, but may last one to two weeks. Fever 99-104, muscular soreness, headache, dizziness and chills are present. Some do not feel very ill, and refuse to be confined. Relapses are common, after a brief period, and may recur after several months at late autumn or early winter. Some have cramps of a severe nature, followed by a sudden expulsion of hard, solid contents, followed by a profuse, violent stream of liquid stools of offensive odor. Subsequently, a few watery stools with loud expulsions of flatus, and the entire condition terminates in twenty-four hours. The person feels relieved, suffering from slight weakness and muscular fatigue.

There are frequently pulmonary symptoms due to upper respiratory infection. The stools are grayish or brown, sour smelling, containing mucus, rarely pus or blood. Here, even when the diarrhea is profuse symptoms of collapse and dehydration are not notably evident.

The feces contain first undigested food particles and later decreasing greatly. The bacterial flora contain nothing unusual, colon bacilli predominate, cocci, rods, staphylococci and streptococcus fecalis. As the diarrhea progresses the bacterial contents diminish.

The blood count is mostly normal, a moderate leukocytosis, rarely large. The vomitus contains HCl at first, but later becomes watery, alkaline, or bilious.

Gastroscopic examination in 35 cases revealed a mild superficial gastritis, reddening of the gastric mucosa, affecting mostly the antral surface, only where the symptoms are pronounced. In mild cases, where vomiting was scant, the mucosa was covered by a mucoid secretion. In recurrent cases, patches of localized gastritis were noticed. The pyloric sphincter was very active and reddened.

The kidney function was not disturbed, although as one would expect, the urinary output was diminished. Albuminuria and cylindruria were faint. A history of previous kidney infection could not be established. The proctoscopic and sigmoidoscopic investigation revealed a hyperemic mucosa in 50% of cases. Tenesmus and rectal irritation were noticeably present. Bacillary and amebic infection could be excluded by bacteriologic finding, severity, pus and blood in the feces and mucosal ulceration.

Food poisoning could be established by tracing the source and history following the ingestion of a certain meal. When there is abdominal pain, shifting to the lower right quadrant, with leukocytosis, appendicitis should be suspected. Even if the pain is not localized at McBurney's Point, and the leukocyte count

is moderate, the possibility of appendicitis should not be overlooked.

Analysis of 2,000 cases seen during the past 16 years discloses that the onset was always sudden, with an incubation period very brief, seldom more than four days. In the great majority of cases nausea, vomiting, diarrhea and abdominal cramp were always present. In a few, one or two of the mentioned symptoms were absent, but diarrhea was always present. Abdominal cramps of a varying degree were almost always present, colicky, generalized, moderate, or severe, and occasionally centered at U. R. Q. or L. R. Q. simulating G. B. involvement or appendicitis. Fortunately, the latter were less than 2%. Fever was almost always present, 99-104. Prostration and dehydration were not encountered to a great degree. As the disease does not last long, and is usually mild, the pain cleared up shortly. Jaundice of a mild nature was present in 4% of the cases. The kidneys were effected in 6% of cases, albuminuria 2 plus to 4 plus, also cylindruria were present. About 20% had coryza, laryngitis, bronchitis, headache, backache, resembling influenza. Cerebral symptoms were in 12%, sluggish reaction of the pupils, headache, dizziness, increased reflexes, irritability, and muscular spasm.

Pain in the lower right quadrant simulating appendicitis during a diarrhea, or enteritis due to various causes is a widely established experience. This is due to an accumulation of offensive, irritating material in the cecal pouch, causing engorgement, which extends to the appendix. The pain, however, is usually mild, often transitory, and not strong on deep palpation. In other words, it is a cecitis. Still one should be on the alert for actual appendicitis, as it happened twice in the mentioned cases. The surgeon stated that the cecum, small and large intestines were unusually hyperemic and that he noticed the same while operating on previous occasions.

Prophylaxis, this term is applicable in the treatment regime, although the real etiology is obscure. There is a strong possibility that the virus is transmitted by contact. Ordinary precautions should be taken in handling the patient, sterilizing utensils, proper disposal of vomitus and excreta. Avoidance of chilling and exposure, during the season when upper respiratory infections prevail. Special care to keep the abdomen warm is helpful. Avoidance of certain foods that cause allergy and indigestion. During the attack, fresh fruit juices, and easily assimilable proteins are recommended. Plenty of water, hot water, half milk and half lime water, lime water, strong cocoa and milk, lemonade, and wine are useful. The food intake should be small at first or none at all, while diarrhea and vomiting are active. Hot applications to the abdomen and rest in bed are useful. If pain is severe a hypodermic of pantopon is advisable. For headache and muscular soreness, aspirin, phenacetin or codein should be used. For the cramps and diarrhea, paregoric ounces II with kapectate ounces II, two teaspoonsful every 1/2 hour until relieved, then every 1-2 hours. Another useful preparation con-

sists of bismuth suballate drachms III, paregoric drachms VI, chloralhydrate drachms II to ounces IV of Lactated Pepsin, drachms II P. R. N. every 1/2 to 1 hours. If dehydration is present, 10% glucose in saline 1,000-2,000 cc. intravenously or Ringer's Solution. For tenesmus paregoric in boiled cornstarch as a retention enema.

Recently, sulphathalidine and penicillin were used with good results. Diluted HCl in water several times daily is of value. An old fashioned remedy which is very efficient, especially if there is suspicion of food poisoning, is Aromatic Sulphuric acid hemotoxylone in syrup of ginger — Drachm one every 1/2 to one hour, and reduced to drachm every 3 hours P. R. N. Some of the atropine derivatives, as belladonna, could be used in conjunction with other drugs.

School pupils may be affected as a group, without traceable source of food contamination. Also homes for the aged, soldiers' barracks, occasionally hospitals, and other institutions have seasonable outbreaks, not developing simultaneously, but in successive crops. There has not been any definite pathology established, whether diffused or localized, affecting the digestive tract. Food elements, overeating, improper food, excessive drinking, or intake of irritating substances, impurities of H₂O, fermentation, altered gastro-intestinal secretions in quality and quantity, excessive bile secretion, or scant bile supply are speculative considerations. Here there are no systemic diseases to favor diarrhea as a secondary factor, with the possible exception of nervous phenomenon.

Acute Ileo-Colitis is more severe. Duodenitis, pain, tenderness, discomfort at U. R. Q. and much bilious vomiting takes place. Jejunum and Ileum inflammation, produces colicky pain, borborygmi, moderate distention, and tenderness over the mid-abdomen. In colitis there is pain, profuse diarrhea, tenderness along the colon and much mucus. Sigmoiditis and proctitis produce much tenesmus, large quantities of mucus, pus, and some blood. Acute gastritis may produce similar symptoms but the diarrhea is not so profuse or common. Pancreatitis is more severe, pain more at epigastrium, radiating to the back, tenderness very marked, great prostration, and the bowel contents are grey, frothy, contain undigested protein and fat. But as a whole this disease runs a milder course, responds better to medication and rest.

CASE REPORT

Case 1. A. F., boy 16, robust, healthy, developed suddenly on December 18, a profuse diarrhea, fever 101, generalized abdominal cramps, vomiting and nausea. There was no history of anything to explain the condition. December 19, the pain shifted to the right, not exactly over McBurney's point. Pain only on deep palpation. Leukocytes 12,500. Appendicitis was suspected and operated the same day. The appendix was large, red, congested. The surgeon stated that the intestines were hyperemic.

Case 2. F. W. boy 18, while on vacation developed diarrhea, cramps and vomiting. The pain remained generalized, but more pronounced over L. R. Q. A physician

was summoned, who gave medication for indigestion. The following day, the parents became alarmed because the condition did not improve, called another physician, who found leukocytes of 18,000. The appendix was found inflamed, soft, and oozing with pus.

Case 3. A. R., man, age 52, building inspector, developed nausea, headache, pain, and rigidity of the muscles of the neck, distressing diarrhea, temperature 99.5. The abdomen was tympanitic, and moderately tender. All physical findings were negative. Blood count 8000, leukocytes. He responded to treatment and rest, recovering in four days.

Case 4. Here are included 48 pupils out of 350 of a preparatory school, ages ranging 16-20. All ate similar food in the school cafeteria, and exposed to the same environment. The sickness appeared suddenly. Almost all had vomiting, diarrhea, nausea, and abdominal cramps. Four were ill ten days, but the rest cleared up in 3-4 days. All had fever 99-102. Seven were jaundiced moderately. The school and medical authorities blamed the milk supply, but were unable to prove it.

Case 5. This embraces 62 members of a soldiers' home of 280, ages ranging 28-87. The situation arose in early January. The older members were affected in a much greater extent, suffering from exhaustion, dehydration, and collapse, requiring stimulation and intravenous medication. Whiskey was given to a good many liberally, which agreed with them. The cardiac, asthmatic, nephritic, anemic, diabetic, arthritic, and paralytic, suffered most. There was a death, one who had an old hemiplegia and a coronary thrombosis. The entire circumstance cleared up in five days, with the exception of 11, who were over seventy and lingered for over two weeks.

Case 6. In this group of 300 in a mental institution of 1200. Here the condition was discovered late. The institution was crowded, short of personnel and isolation could not be installed effectively. The epidemic was checked in less than a week. The same outbreak followed two consecutive winters. The reason could not be definitely established, although the food was suspected. The main symptoms were diarrhea, cramps, and vomiting. One patient developed an intussusception and several had developed rectal prolapse. In sequence, many suffered from weakness in the lower extremities, anorexia, dyspepsia, capricious appetite and choosiness of diet as salty and spicy food articles. A thorough search among the food handlers nothing conclusive was reached. As a matter of fact, they developed the ailment after it was well pronounced among the patients. Nervous depression increased in some, but in many others the drastic diarrheal purge acted as a sobering influence, producing cheerfulness, and mental clearness.

Case 7. In this series are grouped 205 cases, occurring in November 1943. All had the mentioned symptoms, with no serious complications. This took place in an industrial city of 80,000 with a cosmopolitan population. It was noted that the colored population were not affected at all. Pregnant women were also not affected. Laborers predominated. This fact was corroborated by many physicians who came in contact with many cases during the epidemic.

Of course, there are diarrheas caused by multitudinous conditions, as gastrogenic, typhoid, paratyphoid, cholera, arsenical poisoning, avitaminosis, sepsis, thyrotoxicosis, nephritis, cirrhosis of the liver, intestinal disturbances, regional ileitis, ulcerative colitis, beriberi, irritable colon, tuberculosis, etc. But these can be differentiated by various laboratory means well known to the physician.

COMMENT

A large number of epidemic gastro-enteritis cases

were discussed. The salient symptoms are: Vomiting, nausea, abdominal cramps, and diarrhea. There are also other symptoms as fever and nervous manifestation.

It prevails in late autumn and early winter, affecting adults, less frequently the young, and still less young children. Some of the complications are jaundice, dehydration, appendicitis, cecitis, and rarely collapse.

There is no definite pathology or etiology definitely analyzed. The treatment: Rest, diet, astringents, antispasmodics, mild narcotics, and chemotherapy. Although this disease is comparatively mild, subsiding shortly, one should be in constant vigil for unseen and possible complications. It is evident that the natural body defenses are sufficient to resist this disease, but it is up to the doctor, as in many other conditions, to be on the sharp lookout.

The foreign literature, where this disease is more described, has nothing specific to shed light on the subject in any respect, with the exception that the medical profession there is more familiar with this condition, from the diagnostic angle. The treatment they suggest is very rudimentary, relying mostly on Kaolin, Lactic Acid, and alcoholic drinks. This would hardly satisfy the American patients, who have a sense for better and quicker relief. As a final word, it should be stressed that this condition should be carefully treated and should not be considered lightly as an episode of drastic elimination which Nature alone should control. Mild as it may be, the after effects as weakness, loss of weight, recurrence, expose the patient to other complications.

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Editorial

MEGACOLON IN THE NEWBORN

THEODOR EHRENPREIS in Stockholm has studied the subject of megacolon in the newborn and come to very interesting conclusions. He describes how he became interested in this question. A three day old infant was admitted to the hospital with the diagnosis of intestinal obstruction. The child had vomited since the morning of the third day of life and revealed an increasing distention of the abdomen. Some meconium had passed. The child had a healthy appearance. There was no fever. The anus was normal. Some meconium was found in the rectum. The scout film of the abdomen showed large masses of gas outlining the colon. However, the roentgenological examination revealed a colon of nearly normal size and shape. No mechanical obstruction could be found, nor any reason for a paralytical ileus be demonstrated. The author suggested that a Hirschsprung's disease was present without, as yet, showing the typical dilatation of the colon.

In order to clarify this question, the author examined over one hundred healthy children during the first days of life. To his great astonishment, he found the colon in infants full of elongated loops. His roentgenological studies after barium enema show the striking feature of multiple redundancies especially in the region of the sigmoid and the hepatic flexure. Haustrations in these normal children were found to be less frequent and less marked than in adults. The size of the colon showed great variation. Sex-like differences could not be observed. The contractions of the colon and the emptying of the contrast enema were very effective.

Ehrenpreis then discusses the clinical picture of Hirschsprung's disease in ten cases in infants. It constitutes a typical form of ileus previously not described, characterized by obstipation, abdominal distention, and vomiting. The roentgenological signs in megacolon in children are those of gaseous distention (chiefly) of the colon, good tolerance for the contrast enema, and deficient contractile and emptying power of the colon. No mechanical cause of the ileus picture was found. The redundancy of the colon was neither in regard to localization, frequency, nor degree divergent from that of the normal children. The size of the colon and the haustral markings varied within the limits for variations in the normal cases.

Due to the careful examinations of the author, he was able to determine the time, at which the typical dilatation of the colon could be seen in the roentgenogram. The earliest pictures definable as megacolon were seen at the eighteenth day and in another case at the age of three weeks. The slowest development was observed in a patient, who had a colon of normal appearance at the age of one month; however, at the age of three and a half months a dilatation of the sigmoid was recorded.

Ehrenpreis concludes that in megacolon the dysfunction of evacuation is the primary and central factor in its pathogenesis. Malformation and obstruction are questionable causes for this condition. A disturbance of the innervation of the colon appears with great probability to be the cause, but, for the time being it is impossible to define the particular type of this disturbance or even to ascertain its primary nature.

We think that the observations of poor function of the colon without adequate roentgenological findings in the beginning of Hirschsprung's disease in children is also of great interest to all those who are studying the colon in cases of constipation in the adult. The old classification of spastic and atonic constipation, probably, has not been satisfactory to many workers in this field. Many cases are seen in which a contrast enema cannot be evacuated, but, without any other roentgenological pathology. The haustral markings were normal, there were no elongated intestinal loops visible. Even the administration of a soap sud enema had only a very poor effect. Most of those patients suffer predominantly from a general malaise as soon as their bowels fail to function. We have asked ourselves very often, how to explain

this phenomenon and have come to the conclusion that these patients must have some kind of a neuromuscular disturbance in the colon. The question arises if those findings in children as observed by Elhrenpreis as early symptoms of megacolon could tie in with the many unexplained findings in adults. Could it be that there are more cases of *forme fruste* of megacolon than we generally realized? Are certain types of constipation in adult patients perhaps due to an abortive form of megacolon? Is there a clinical entity of "abortive megacolon"?

Franz J. Lust

REFERENCE

Elhrenpreis, Theodor. Megacolon in the newborn.
Acta Chirurgica Scandinavica, V. 94, supplement 112, 1946.

Book Review

TEXTBOOK OF ENDOCRINOLOGY. By Hans Selye, M.D., Ph.D., Pp. 914, (\$10.25), University of Montreal, Montreal, Canada, 1947.

The author has written this large volume as a standard textbook of endocrinology and its fullness and excellence brings to mind by contrast some of the books published only twenty years ago in which, owing to lack of factual data, the narrative consisted chiefly of theory and supposition. In the present volume we have passed the stage of speculation and come upon the more solid ground of clinical and ex-

perimental reports which are tabulated and coordinated with signal skill and illustrated profusely with half tone engravings. It is perhaps impossible to render the slightest adverse criticism of this volume, inasmuch as it completely serves the purpose for which it was written. The final section on the "general-adaptation-syndrome" and the diseases of adaptation is highly original and provocative and betrays a very synoptic and dynamic application of endocrinologic knowledge.

Abstracts Of Current Literature

ABSTRACT EDITOR — M. H. F. FRIEDMAN

Jefferson Medical College

1025 Walnut Street

Philadelphia, Pennsylvania

CLINICAL MEDICINE

MOUTH AND ESOPHAGUS

BROWN, C. J. O.: *Surgical treatment of carcinoma of the esophagus (report of three cases)*. (Med. Journ. Australia, July 5, 1947, V. II, No. 1, 10-12).

Transthoracic oesophago-gastrectomy with oesophago-gastrostomy presents a practical approach to the problem of carcinoma in the lower two-thirds of the oesophagus or in the cardiac end of the stomach. It is probable that total gastrectomy is more readily performed by this route than from below. Patients

tolerate the operation very well; and, even if the growth recurs, they have a period of relief and are saved the distress of death from starvation.

DREIZEN, S., MANN, A. W., SPIES, T. D. AND SKINNER, T. A.: *Prevalence of dental caries in malnourished children*. (American J. Dis. Child., Sept. 1947, V. 74, No. 3, 265-273).

The surprise in this investigation was the unexpected result. No known theory of dental caries explains the fact, herein discovered, that children fed an inadequate diet since infancy have an incidence of caries only 44.46 per cent as high as that of a

corresponding group of children fed an adequate diet during the period of growth and development of their permanent teeth.

BOWEL

OTTENHEIMER, E. J.: *Cancer of the rectum. Analysis of cases in Connecticut 1935-1945.* New England J. Med., V. 237, p. 1, July 1947).

Cancer of the rectum has sufficiently well-recognized signs and symptoms which should make its recognition relatively simple. Biopsy examination should always be made when there is any doubt. Operability, morbidity and mortality statistics show constant improvement. These statements are based on data pertaining to 1610 patients with cancer of the rectum who were admitted to hospital in the eleven year period 1935-1945. The improvements in the surgical treatment may be attributed to wider use of antibiotics for clearing the operative field, employment of competent medical anesthetists who understand the problems encountered, and the recognition of the stages of shock and its managements. Still further improvement in end results is to be expected. The five year cure rate of 7.9 per cent of all cases obtained in 1935-1940 is still far too low.

D. A. Wocker

TENER, R. J.: *Lipomas of the large and small intestine, (A clinical and pathological study of twelve cases which produced symptoms necessitating surgical intervention).* (Journal-Lancet, January 1948, V. LXVIII, No. 1, 12-23).

Lipomas occur chiefly in the large bowel and at an average age of 53. Pain, vomiting, diarrhea, constipation and weight loss were the chief symptoms. Ulceration of the mucosa covering the lipoma was present in all but one case. Such lipomas are submucous, intramucosal, intermuscular and subserous in origin. The diagnosis is practically never made pre-operatively and in many cases the pre-operative diagnosis is that of malignant neoplasm. Treatment is surgical.

ABRAMSON, H.: *Infection with salmonella typhimurium in the newborn.* (Am. J. Dis. Child., Nov. 1947, V. 74, No. 5, 576-586).

A variable clinical picture is produced by the Salmonella group of enteric pathogens in the newborn, as shown by a study of three related outbreaks. Early stool cultures should be made in all cases of suspected or early diarrhea. Newborn infants are highly susceptible to infection with Salmonella organisms. The oral administration of streptomycin is of value in altering the bacterial flora and preventing spread of infection.

BOHLS, S. W.: *Laboratory aids in the diagnosis of infectious diarrhea in children.* (Texas State J. Med., January 1947, V. XLIII, No. 9, 575-577).

The dysentery mortality rate in Texas is more than twice as high as the average of the United States and the disease occurs chiefly in children under two years of age. Tetrathionate enrichment media allows for a greater percentage of isolation of the enteric pathogens, and for the isolation of the unusual microorganisms. Cultures and complete fixation tests now are routine procedures in the diagnosis of *Endameba histolytica* infestations. Material for virus studies and identification must be submitted in a frozen state to the virologist.

CUNNINGHAM, N.: *Splenoptosis and transposition of the colon.* (Med. J. Australia, Oct. 11, 1947, V. II, No. 15, 451).

An infant of six months presented a palpable mass in the left upper abdominal quadrant whose edge felt like the spleen. X-ray examination of the colon showed it to be transposed with the descending colon on the right side and the cecum on the left. It turned out to be a ptosed spleen. The presence of transposition of the colon may indicate an abnormality of the phrenicoceolic ligament, which would explain the splenoptosis in this case, since this ligament normally helps to hold the spleen in place.

JACKMAN, R. J.: *Submucosal nodules of the rectum: diagnostic significance.* (Proc. Staff Meet. Mayo Clinic, Oct. 29, 1947, V. 22, No. 22, 502-504).

Small, submucosal nodules, palpable on routine digital examination of the rectum are a fairly common finding. Usually they are disregarded as being inconsequential. Although most of them are the result of injection treatment or of benign nature, a sufficiently high percentage (6.9 per cent in a series of 87 cases) are malignant to warrant excision and microscopic examination.

HOJENSGARD, I. C.: *Constipation caused by megasigmoid treated by sigmoid resection.* (Nordisk Med., Sept. 12, 1947, V. 35, No. 37, 1881-1884).

Obstinate chronic constipation which is resistant to every kind of medical treatment is sometimes caused by a megasigmoid. Such cases, moreover, are very often complicated by volvulus of the sigmoid, either acute, total, or periodical, spontaneously remitting.

In acute cases reposition of the volvulus by the introduction of a tube under X-ray control should be tried, in order to put the patient in a condition more favorable for operation. Should this prove unsuccessful, a sigmoid resection should be performed (and not, e. g., merely a detorsion). If the bloodless reposition is successful, the patient should be operated upon later on. Also megasigmoid patients with invalidating constipation should be offered a sigmoid resection, even if there are no instances of volvulus in the history.

Six patients were operated on for megasigmoid, all of them with chronic obstinate constipation, three of them at an acute stage with volvulus. All were cured, the constipation and attacks of pain ceasing.

Peptic Ulcer and Pregnancy

Four Cases and a Review of the Literature

By

S. P. BRALOW, M.D.

S. SCHEINBERG, M.D.

and

H. NECHELES, M.D., Ph.D., F.A.C.P.

CHICAGO, ILL.

IT IS ACCEPTED GENERALLY, that pregnancy exerts a favorable influence on peptic ulcer; new ulcers develop rarely during pregnancy, and ulcers that existed before pregnancy have been reported to heal or not to recur during a pregnancy (1, 2). These experiences have been generalized and not infrequently the possibility of an ulcer in a pregnant woman with upper abdominal complaints is ruled out, and a false sense of security has developed concerning dangers from complications of peptic ulcer during pregnancy. Obstetric hospital records have been used by a number of authors for statistical surveys (3-5). To use such records for a disease not related to obstetrics may be objectionable, however. Not only are such records mostly restricted to obstetrics, but abdominal complaints during pregnancy are usually ascribed to the pregnancy or to the mental condition of the patient.

No cases of peptic ulcer in relation to pregnancy were found in the cross index system of Michael Reese Hospital. However, on inquiry among staff physicians and among patients, four cases were found easily, with peptic ulcer complicating pregnancy or puerperium. Although this number is small, and although our inquiry revealed a larger number of cases in which peptic ulcer improved during pregnancy, we want to stress the point that peptic ulcer can occur in severe forms in connection with pregnancy and may threaten the life of the patient.

Many theories have been offered during the last fifteen years to explain the absence, the healing, or the inactivity of peptic ulcer during pregnancy. The present discussion of the literature covers the following categories: mechanical effect of the pregnancy itself; chemical changes during pregnancy; observation of ulcer incidence at various periods of hormonal changes; hormones in ulcer therapy; and four cases of pregnancy complicated by peptic ulcer.

The mechanical theory for the alleviation of symptoms of peptic ulcer during pregnancy was proposed by Hurst and Stewart (1). They believed that the support offered to the stomach by the rising uterus relieves the strain on the lesser curvature of a long stomach. This in turn, improves gastric circulation, promoting healing of an ulcer. However, our clinical observations indicate relief of symptoms as early as in the first trimester of pregnancy. This would be difficult to explain on the basis of support from a relatively small uterus.

Concerning the effects of hormones* on gastric motility, we have found the following in the normal dog: ovarian extract Lilly and corpus luteum extract Lilly gave doubtful results. Ovarian substance without corpus luteum Lilly intramuscularly, together with daily oral doses of anterior pituitary substance Lilly produced significant increases of hunger contractions in 7 out of 9 tests (6). In estrus and in early pregnancy in the dog gastric emptying times were prolonged definitely, while in the later stage of pregnancy emptying time returned to normal (7). During menstruation increased motor activity of the stomach has been observed (8).

Balint (9) has suggested that the blood and the tissues tend to be acid in patients with peptic ulcer and that they tend to become alkaline during pregnancy. Hurst and Stewart (1) felt that decreased gastric acidity may play a role in alleviation of symptoms during early pregnancy. The few studies on gastric secretion during normal pregnancy are uniform in showing a high incidence of diminished or absent free HCl. Nakai (10) found 14 normal women showing a greater decrease in free acidity in the first than in the second half of pregnancy. Arzt, in two different studies (11, 12) and Mason (13) noted a decrease of acidity in the pregnant individual when compared to non-pregnant controls. Strauss and Castle (13a) found in 24 normal women, between the third to sixth month of gestation, a 50% decline in free acidity from the maximum level noted at any other period during the pregnancy. In the last month of pregnancy acidity rose again, and post partum it

From the Department of Gastro-Intestinal Research Medical Research Institute of Michael Reese Hospital, Chicago.

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* In the following the potency of some of the various hormone preparations used, could not be evaluated.

was two to three times higher than during the sixth month, when the greatest decrease was seen.

In evaluating these data, one must consider the findings of Bloomfield and Keefer (14), that repeated gastric analysis on the same pregnant individual even lacks the degree of relative constancy seen in non-pregnant women. We want to stress also, that anemia occurs frequently in pregnancy, and this may explain part of a decreased acid secretion.

Alvarez and Hosoi's (15) work on the intestine of pregnant rabbits showed that the gradient of irritability was decreased in some and reversed in others, and rhythmic contractions were slow in all experiments. Duff Allen (16) felt that low gastric acidity during pregnancy might be due not to an actual decrease in HCl secretion, but to neutralization by regurgitated duodenal juice. He found that the gastric contents with low free HCl contained a normal or possibly increased amount of total chlorides. He believed that reverse peristalsis caused regurgitation, and that this was due to a reflex from the early pregnant uterus, as suggested by Alvarez (15). Strauss and Castle (13a) disagree with this, because they found no bile in the gastric juice of their pregnant subjects.

In contradistinction to pregnancy, the menstrual cycle has no favorable influence on ulcer symptoms. In fact, occasionally ulcer pain is increased before and after menstruation. Hess and Faltitschek (8) observed greater motor and secretory activity of the stomach during menstruation, which they believe may aggravate ulcer symptoms. Sutherland (17) has pointed out that recurrent hematemesis from ulcers seems to occur with greater frequency during the menstrual period, and that visceral congestion during the period may be a contributing factor. However, we have to consider nervous tension as an important factor in any discussion on aggravation of ulcer symptoms, particularly in connection with menstruation.

Winkelstein (18) reported on a fairly large group of patients who, at the natural or artificial menopause, experienced the onset or exacerbations of a peptic ulcer. Both Crohn (2) and Hurst (1) agreed with this observation, and the latter pointed out that, if any change is observed, it is toward aggravation of pain with the tendency for the general health to be more affected by local conditions than before. Like in menstruation, we have to consider nervous tension by itself as an ulcer factor in menopausal women.

Relapses in ulcer patients during and after lactation was noted by Crohn (2) and was supported by the results of experiments by Klein (19) and Hollander (20). The latter demonstrated that acid secretion from gastric pouches in the dog increased markedly during lactation and that ulcerations of the abdominal wall around the stoma of the pouch developed or increased markedly during this period. These observations led Winkelstein (21) to incriminate prolactin, the lactogenic anterior pituitary hormone, production of which is increased during lactation. Dur-

ing pregnancy prolactin formation seems to be inhibited by a high concentration of ovarian or placental hormones in the blood, but with the fall in the concentration of these hormones at the end of pregnancy or immediately post-partum, prolactin stimulates mammary secretion (22, 64).

Saltzstein et al. (3, 4) found a high incidence of endocrinopathies (46%), especially of the pituitary-gonadal-thyroid type, in a series of 30 female ulcer patients. In normal female ulcer patients reproductive function was not affected by the presence of an ulcer.

The sex ratio, and the distribution of peptic ulcer between stomach and duodenum, seem to have undergone considerable changes during the last 50 years, but a discussion of this seems to be beyond the scope of the present review (24, 24a, 25).

The original idea for hormonal therapy was based on favorable effects of injection of female blood in cases of gastritis and ulcer. Young girls with atrophic gastritis were treated with follicular hormones with supposedly beneficial effects (26). Korbach (27) was the first to treat four men with gastric ulcers with injections of folliculin in addition to diet and ascorbic acid, with reportedly good results. Likewise, Csepai (28) noted no recurrence in 47 of 51 cases treated with folliculin but with no special diet. Boggian (29) reported good results in patients with duodenal ulcer, and Parade (30) noted most of his 40 cases were free of complaints following three or four injections. Tangari (31) claimed that follicular hormone increased markedly the thickness of the gastric mucosa of the guinea pig, and that the appearance of numerous fibroblasts in the mucosa indicated increased facility of healing and scar formation. Schittenhelm (32) warned against the use of follicular hormone in cases of bleeding ulcers, because it produced hyperemia.

Schulz (33), Mathe (34), and Larizza (35), reported good results with estradiol benzoate or estradiol propionate in both male and female ulcer patients. Engel (36) noted that 9 women with hyperacid chronic gastritis had increased symptoms 8-10 days before the menstrual period and he reported therapeutic results with perlingual estradiol benzoate. Albers (37) investigated the effects on gastric acidity of estradiol benzoate in 84 normal women. Secretion was either unaffected or increased transiently. Stilbenes seemed to raise acid secretion.

Focken (39), Bock (40), and Schulz (41) used testosterone propionate for gastric and duodenal ulcers and claimed good results. In the case of testosterone therapy we have to ascribe a large part of its effects to general tonic and nitrogen retaining properties of this drug. Parade (30) had the impression that in cases of ulcer in the male, the effects of follicular hormones were better than those of testosterone.

Winkelstein (42), continuing the studies of Klein (19) on the relation between sexual cycle and ulcerations around the stoma of gastric pouches in dogs,

noted that such ulcerations healed completely during oestrus. Reasoning that ovarian follicular hormone was chiefly responsible for oestrus, he treated dogs with stomal ulcerations with Theelin and found them to heal within ten days. In an attempt to duplicate increased peristomal ulceration during lactation, male and female dogs were injected with anterior pituitary extracts with the result that the ulcerations grew worse. In 20 cases of menopausal exacerbations of peptic ulcer. Progynon B was given three times a week for three weeks (21). Symptomatic improvement was noted, but no change in most of the acidity tests. In evaluating this subjective relief, one must consider the known general improvement of menopausal symptoms by estrogen therapy, and the frequent relief of nervous tension, which by itself may account for improvement, so that one need not assume a specific hormone effect on peptic ulcer.

Abrahamson, Church, and Hinton (43) treated 22 men with histories of chronic duodenal ulcer for at least one year, for 18-30 days, with daily intramuscular injections of various dosages of Theelin in oil. They found a higher percentage of remissions as well as roentgenologic evidence of improvement than in controls. However, 3-12 months later, there was no difference in therapeutic results between the treated and the control series. Again, we have to stress psychic effects of any therapy in peptic ulcer.

Sandweiss, et al. (44) used Mann-Williamson dogs to study the role of hormones in the decreased clinical incidence of ulcers during pregnancy. Fifteen animals were treated with Theelin, and all died sooner than the controls. Another 15 were treated with anterior pituitary-like hormone, Antuitrin-S. Of these, 53% showed no ulceration, and four out of seven showed signs of healing of ulcers. Thus in 80% of the animals the typical jejunal ulcerations was prevented, healed or healing. Farbman et al. (45) found that neither pregnancy nor Antuitrin-S or pregnancy per se significantly protected dogs from cinchophen ulcers. The variation between his control values and those of Reid and Ivy (46) and of Slutsky (47) may have been due to the well known differences between brands or batches of cinchophen.

Sandweiss et al. (48) treated 18 patients with active symptoms of proved peptic ulcer by daily injections of 2 to 5 cc. of APL hormone (Antuitrin-S) for 14 days. 78% of these patients were benefited, but the authors did not believe this therapy afforded any greater beneficial effect than other injection therapy of peptic ulcer. Antuitrin had no effect on free and total acid secretion either in human or dog.

Culmer and Ivy (49) studied the anterior pituitary-like fraction (APL) of human pregnancy urine, because in the human it is produced in great quantity during the earlier period of pregnancy when gastric secretion is reported most depressed. However, the achlorhydria reported to occur not infrequently during pregnancy in women, has not been observed in the dog. APL apparently is not produced in the dog. The

results on seven non-castrated female dogs with Pavlov pouches given APL fraction of human pregnancy urine by injection 1/2 hour before feedings showed a depression of gastric secretion. These results were interpreted as suggesting that the effective substance or substances in the APL fraction acted on the parietal cells both directly and indirectly, chiefly directly. That estrone did not change gastric acidity was observed by Atkinson and Ivy (51) on dogs and in man, and by Schiff, et al. (52). This is contradictory to results obtained by Winkelstein (42). Manville and Munroe (23) found that corpus luteum had no effect on gastric secretion.

Way (65) in studies on the human has found that gastric acidity varied inversely with the concentrations of anterior pituitary-like factor found in the urine.

The relations between anterior and posterior lobe secretion of the pituitary gland and the role of the latter in pregnancy are not well known. Posterior pituitary secretion seems to affect gastric secretion and may play a role in peptic ulcer (53-60).

Szenes (61) found 12 gastric and 7 duodenal ulcers in pregnant women in the literature up to 1924. From these few cases he drew the following conclusions: nulliparous patients come to operation for ulcer at an earlier average age than those who have had one or more pregnancies; ulcer patients who improve during pregnancy are those who have had little or no vomiting during the course of the pregnancy, while those who do not improve or get worse, have frequent vomiting episodes. Lastly, since in only 10% of his cases ulcer appeared at the time of menopause, he concluded that: "this small percentage speaks for the fact that the ovarian function plays a role in the genesis of ulcer."

Mussey (5) reported 370 operations of necessity during pregnancy over a period of 10 years and only 2 were for peptic ulcer. Saltzstein et al. (3, 4) reviewed the records of 70,310 consecutive hospital admissions during pregnancy and found only one case of a complicated ulcer. This patient died of a perforated duodenal ulcer after a still birth at 6 months; hormonal imbalance may have been a causative factor for both, the still birth and the perforation of the ulcer. In contradistinction to the low incidence of peptic ulcer was the relative high incidence of other gastro-intestinal disorders in this large series. A case of peptic ulcer complicating a pregnancy was reported by Mulsow and Brown (62) in 1936. Their patient was a 41 year old white female who in the 35th week of gestation developed hematemesis and melena. She died 10 hours after delivery and the post-mortem diagnosis was hemorrhage from a duodenal ulcer and obstetrical shock.

Jones (63), among approximately 10,000 confined women in London, England, found only one with a slight hematemesis, but no ulceration could be demonstrated. Among over 2,000 women admitted with abortions only, one had hematemesis associated with

renal failure. Jones states that the acute anxiety of pregnancy in unmarried women does not precipitate gastro-duodenal hemorrhage.

In the period covering the last 25 years at the Michael Reese Hospital, 4 cases of peptic ulcer complicating pregnancy were found.

Case 1: A 22 year old white female was delivered on June 15, 1925 at the Chicago Lying-In Hospital after an uncomplicated pregnancy and labor. On the fifth day post-partum, she suffered a gross hemorrhage from the gastro-intestinal tract which was described as filling two bed pans. Her past history revealed no ulcer symptoms or previous hemorrhage. After the routine supportive therapy she was maintained on an ulcer regime for two months and then a partial gastric resection was performed at Michael Reese Hospital, which revealed an active duodenal ulcer.

Case 2: A primiparous patient was delivered normally at Michael Reese Hospital in 1935. She had an uneventful post-partum course and was discharged on the 10th day. During her first night at home she had a large gastro-intestinal hemorrhage and was brought back to the hospital in a state of approaching shock. She was given transfusions and conservative supportive therapy. The clinical diagnosis of a bleeding peptic ulcer was made, and she was treated accordingly. Two months later upper gastro-intestinal X-ray failed to visualize an ulcer and she has been free of symptoms ever since. She had no previous history of peptic ulcer.

Case 3: A normal white female, 38 years of age, slender, underweight, and highstrung. At 23 years of age, she suddenly felt faint and dizzy like a "dismount", and perspired profusely. An active, bleeding duodenal ulcer was diagnosed clinically and roentgenologically. For the next eight years she had periodic epigastric distress and heartburn, and at night awoke sometimes with pain. Amphojel gave her relief, but was constipating. At the age of 31 she became pregnant and her ulcer distress, heartburn, and night pain increased, particularly during the first three months, but continued until the end of the pregnancy. During this time, she took large amounts of amphojel, even in the delivery room. After delivery, ulcer symptoms disappeared and did not return at a second pregnancy at 35 years of age.

Case 4: A 29 year old white female patient had a peptic ulcer diagnosed by X-ray, for which she had been under treatment for the last seven years. In March, 1946 she delivered a healthy baby, but described attacks of nausea, vomiting, and epigastric pain during the last trimester of her pregnancy, which she ascribed to pregnancy. The attacks persisted post-partum and on May 4, 1946, she complained of tiredness, dizziness, backache, vaginal discharge, and occasional rectal bleeding. Pain was described as being usually sharp and localized in the epigastrium. The pain was most severe two hours after meals and was relieved by milk and cream. Her history revealed similar complaints during a previous pregnancy four years before. Fluoroscopy visualized a scarred duodenal ulcer with tender and irritable bulb. No evidence of bleeding was noted.

In summary of these four cases it is interesting to note that only 2 had previously diagnosed ulcers. The two who had no previous history developed severe hemorrhage between the fifth and tenth day post-partum, and almost exsanguinated. In Case 2 we have only clinical evidence of peptic ulcer. The onset of the hemorrhage seems to have occurred in the two post-partum patients at the time when lactation becomes active, and after the acute episode the patients became

asymptomatic. The other two, who were known to have had ulcers had no other serious complications besides the epigastric pain which was fairly well controlled on routine ulcer regime.

DISCUSSION

The usual explanation for the frequently observed clinical improvement of peptic ulcer during pregnancy is that the gastric acidity is diminished, particularly between the third and sixth month of gestation. The reason for this decrease is not known, and certain hormonal effects have been considered. However, various investigators have failed to show consistent changes in gastric acidity with either estrogenic or anterior-pituitary like hormones.

Recently, enterogastrone and urogastrone and a factor contained in both, antheilone, have been used in the treatment of peptic ulcer in man and dog. The pituitary gland has been suspected to play a role in the production of urogastrone. The antheilone effect of urogastrone does not seem to be due to prolactin (50).

The possibility that an anti-ulcer factor in the APL fraction is antheilone cannot be ruled out definitely. Urogastrone was found diminished in the urine of patients with peptic ulcer. The possible relationships between antheilone and urogastrone and enterogastrone await further study (66).

Many hormones have been tried clinically on ulcer patients with reportedly good results, but one fails to see significantly better results than with ordinary medical regime as used commonly, except for effects on the general health and mental status of the patient.

The close relationship between hormones and vitamins (43) may play a role in the question of peptic ulcer in pregnancy, because some of the endocrine secretions are dependent on the availability of vitamins for their synthesis or action.

The four clinical cases of ulcers complicating pregnancy which we present are difficult to analyze as far as incidence is concerned. Three of our cases were obtained from staff physicians of Michael Reese Hospital and the fourth case had come to our own attention. Two of the ulcer cases occurred during pregnancy, and two shortly after delivery. In the latter two the clinical impression of Crohn (2) and the findings in dogs during lactation, quoted above, may lead the way for further work. The cause of aggravation of ulcer symptoms during pregnancy is unknown.

The severe episodes of hemorrhage occurred in the patients with no history of ulcer. Thus the obstetricians should keep such a possibility in mind and should not ascribe too readily the occasional heartburn and epigastric distress complained about by their patients to the pregnancy per se. Such a feeling of safety we believe to be dangerous, because the few cases which occur from time to time may jeopardize the life of a patient.

SUMMARY

It has been believed for many years that during

pregnancy peptic ulcer rarely appears, rarely flares up and often heals.

Gastric acidity tends to be decreased during pregnancy, but theories of mechanical and humoral factors producing this decrease are vague.

Four clinical cases of ulcer complicating pregnancy are reported, of which two, with no previous ulcer history, had serious episodes of hemorrhage.

We believe that obstetricians should not feel safe

in view of the reported rarity of the co-existence of peptic ulcer and pregnancy, but should study carefully all case of persistent heartburn, epigastric distress, etc., in their patients, as peptic ulcers may produce serious complications during or shortly after pregnancy.

It is felt the number of ulcers observed in pregnancy may increase if the obstetrician is impressed with their possible co-existence and keeps this in mind, when obstetric patients complain of symptoms that may be due to pregnancy as well as to peptic ulcer.

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Dysentery, Colitis and Diarrhoea in Japanese Civilian Prison Camps in the Philippines during World War II. I: Primary, Concurrent and Recurrent Dysentery

By

FRANK G. HAUGHWOUT*

NEW YORK CITY

INTRODUCTION

IN THE SERIES OF ARTICLES, of which this is the first, the writer will undertake to set forth the salient features of a rather unusual study of intestinal disorders as they occurred in a group of prisoners of war in Japanese Civilian Prison Camps in the Philippines during World War II. In the course of the work, diagnosis was made and treatment carried out on more than 2,000 persons. Of the three deaths occurring among this 2,000, not one was of diarrhoeal disorder. A clinical and microscopical study was made of all these patients, and records and pathological specimens, hidden during the course of the studies, were brought back to this country. It probably is the first instance in which it was possible to make such studies in a war prison camp. The internees studied were of a group of persons who entered the camps in a state of general good health and nutrition. Observations on them were continued without interruption until the day of their liberation by the armed forces of the United States, more than three years later. For some time previous to liberation the food intake had been reduced to between 600 and 700 calories per capita, per day. The majority of the internees were then in a greatly depleted physical condition and had suffered severe loss in weight. These studies record the progressive decline in function and resistance of the alimentary tracts of, and the intercurrent intestinal disorders sustained by, these people during imprisonment.

My staff associates were Drs. Beulah Ream Allen and Dorothy Kenney Chambers. They carried the greater part of the bedside work, with never flagging energy and courage. I owe a great debt to these two able physicians without whose loyal and unstinted support my program could not have been carried out. Our clinic was open 24 hours a day, at least one of us being on call at night.

The work was carefully planned before the war. Equipment was reduced to the bare essentials that could be smuggled into the camp. Efforts were made to foresee every contingency that was likely to arise. So successful was this effort that no material or records of importance were lost; the story was brought back to this country intact. We established our clinics for the diagnosis, treatment and studies of intestinal disorders at Camp Holmes, Baguio and, later, at Santo Tomas Camp in Manila. These clinics were separate from the general camp medical and surgical clinics and were administered by our own staff. We limited our work to intestinal disorders and took over general medical and surgical

work only in times of great emergency. The organization of these clinics has been set forth in other publications (1, 2, 3) and need not be detailed here.

Aside from the work of relief, what it was most desired to prove in our enterprise, was the entire practicability and reliability of the methods of differential diagnosis of the dysenteries and diarrhoeas through the microscope, and the dependence that can be placed upon them even under exacting and trying conditions. The opportunity presented to study the war time incidence and course of bowel disorders under conditions of virtual military control, in a group of people who could be held under constant observation over a long period of time, was too exceptional to be disregarded. At the conclusion of the work, it may be said that the methods of cytodiagnostics met every issue presented to us in our clinic. In most instances, we were able to determine and carry out treatment within an hour or two of the time the patient reported to us. Moreover, it was possible quickly to detect developing recurrence, secondary processes and complications. In this manner we maintained our mortality at zero. In other camp clinics, where these methods were not employed, the results were not so happy.

In a short article it is, of course, impossible to go into the minutiae of cytodagnostic methods, but I have explained them fully elsewhere (5). The history of the development of these methods goes back to 1912 when Bahr (6) figured and described his observations on the cytology of dysenteric stools in the Fiji Islands. During World War I, Willmore and Shearman (7), made a thorough study of these exudates and defined their specific characters in a paper published in 1918. The British immediately followed the lead of Willmore and Shearman. I first took up the work in the Philippines in 1919 and have since published numerous papers among which five may be cited here (8, 9, 10, 11, 12). In a field manual for the British medical services in the Far East (3), I summarized the subject up to 1924. This book was adopted as the standard text for the hospitals and laboratories of the U. S. Army in the same year, which placed the subject before American physicians. Important papers subsequently were published in this country by Callender (13, 14, 15), and Callender and Inmon (16). However, little on the subject has found its way into the clinical journals here and for that reason relatively few American physicians know of these methods or of the valuable time that is thus saved in making a diagnosis in bowel disorders.

The secret of success in the treatment of the dysenteries and their kindred affections, and the control of their sequelae, lies in getting off to a good start.

Most of the difficulties that arise in the handling of acute diarrhoeal disorders and their complications are the result of failure to define the nature of the process at its onset and act accordingly.

Those who undertake the study of the dysenteries

*Late Consultant, U. S. Army Institute of Pathology. Formerly Professor of Protozoology and Chief, Department of Parasitology, Graduate School of Tropical Medicine and Public Health, University of the Philippines; Chief, Section of Parasitology and Cellular Pathology, Bureau of Science, Manila (Retired).

and diarrhoeas on a broad, comparative basis, sooner or later are impressed by three salient characteristics common to all. 1. The comparative ease with which they can be brought under control in the beginning. 2. Their tendency to resolve themselves into more or less protracted chronic processes if the primary access gets out of hand. 3. The interlocking activities that may, on occasion, arise between them and the confusions and misconceptions to which these concurrent conditions may give rise.

Any acute diarrhoea presents at least a dozen possibilities as to etiology. These must be explored before an accurate diagnosis may be made. In most cases, the evidence leads to one cause and it becomes a comparatively simple matter to apply the treatment that experience has taught will most effectively combat this particular cause. Not infrequently, it will be found that two, or even more, causes are concurrently operating. Each must be fought, not only as a separate entity, but also in the light of its collaboration with the others.

In bacillary dysentery, the infection starts superficially in the mucosa. It tends to spread rapidly as a localized inflammatory process. If this infection is promptly recognized for what it is, and checked then and there by appropriate therapy, it subsides and the damage is soon repaired. In cases of amoebic dysentery, if the amoeba, and the local reactions of the bowel wall to them, are recognized before secondary inflammation becomes extreme, the acute process may be brought under control by a joint attack on the amoeba and the secondarily invading bacteria.

In the non-inflammatory diarrhoeas, the underlying stimulus is manifest as a response to chemical or mechanical irritation of the mucosa. Further study usually will reveal the nature of this irritation, and dietetic and other measures can be instituted that will remove its cause and give the bowel freedom to readjust itself to normal conditions. This it usually will do once the source of irritation is withdrawn.

In short, the prime requisite is early and accurate differential diagnosis and the prompt and sustained application of the treatment indicated by the diagnosis. Only thus may treatment be started at the time it will be most effective — the onset of the disturbance. We have applied the principles of first aid to the relief of acute bowel disturbance. We have succeeded in getting off to a good start.

However, if these things are not accomplished, the system breaks down. A prolonged and discouraging campaign may ensue against a foe that can be expected to avail itself of every means of ambush, dissimulation and deceit.

DIAGNOSIS

The question now arises as to what means we have for making an early differential diagnosis in the diarrhoeal affections. There are three approaches — clinical, bacteriological and microscopical; let us consider them.

Clinical — Fortunately, there are few men to-day who believe that accurate differential diagnosis of these conditions can be made by clinical methods. In the more intense of the non-inflammatory or irritative conditions, the physical reactions of the patient are difficult to distinguish from the reactions produced in typical dysentery. Moreover, the stools may be mucoid, cell-laden and blood-streaked. Controlled studies in the camps have shown that blood-streaked, mucoid stools are *not* pathognomonic of dysentery.

The frequency of their occurrence in non-dysenteric conditions has effectually disposed of this ancient criterion. Conversely, the stools of early bacillary dysentery usually are devoid of macroscopic blood. Erythrocytes always can be found microscopically; but gross blood seldom appears until the process has extended beyond the superficial layers of the mucosa. The greater number of bacillary dysenteries run a mild course; elevation of temperature is likely to be slight and so evanescent that by the time the physician sees the patient it may have fallen to normal. Such cases often are dismissed as "simple diarrhoea" and go untreated: They are dangerous in that sufficient injury may have been done to the gut wall to lay down the foundation for an elusive post-dysenteric colitis. Therein, lies the explanation of why the clinical diagnosis of bowel disorders has fallen into disrepute.

Bacteriological — In the event of failure to demonstrate *Endamoeba histolytica* in the stools of a patient suffering from diarrhoea, it has become customary to fall back on the bacteriological findings as a guide to treatment. Many physicians will not accept any other diagnosis. In fact, bacteriology seems to be the sole recourse in most laboratories in this country.

I have no wish to depreciate bacteriology in the study of intestinal disorders. It has been, and still is, of the greatest value in the advancement of our knowledge of the etiology and epidemiology of these conditions and it still holds an important relation to the management of certain phases of the diarrhoeal problem. I emphatically say, however, that it cannot meet the issue presented by the problem of bringing early and accurate diagnosis and treatment to the patient. Much is claimed for recent advances in the cultivation of bacilli of the dysentery group and there is no doubt of their value; but the fact remains, that it takes time to grow the organisms and differentiate them from others. Those hours may mean much to the welfare of the patient. In that time he goes untreated and many suffer serious damage. From the very practical viewpoint of treatment, it makes no difference what species or strain of *Shigella* is involved in the case. One need only know that the dysentery is of the bacillary type and that is very easy to determine microscopically. Moreover, failure to isolate the dysentery bacillus in culture, does not rule out bacillary dysentery. The factors that contribute to this failure are too well known to require discussion here. When treatment is started on the basis of an early microscopical diagnosis the patient usually is well on the road to convalescence by the time the bacteriological report is received from the laboratory.

However, there is no reason why the clinician should not seek bacteriological confirmation of a diagnosis made by other methods. While it may, in some instances promote vacillation, that practice is rather to be encouraged, for from the results he is likely more quickly to appreciate the uncertainty and the time that is lost by dependence upon bacteriological methods to establish an early and reliable diagnosis. Negative

reports too often give the clinician a false sense of security. One never really knows if it is a true or false negative. They are responsible for many cases of chronic colitis that often long elude diagnosis.

Microscopical — This is a procedure in cytodiagnosis. It is the method of choice if one wishes to nip an acute intestinal disturbance in the bud. It is based on a study of the reaction of the intestinal wall either to an inflammatory or an irritative process. Broadly stated, the cellular pattern that appears in the bowel discharges, is a replica of the histopathology of the existing process. It is, in the strict sense, a biopsy without instrumental intervention. The findings are quite as distinctive and dependable as are those in haematology, tumor diagnosis, pulmonary and other exudates and transudates, and the more recently advanced vaginal cytodiagnosis. It calls for neither more nor less skill than is required in the execution and interpretation of other procedures in cytodiagnosis. It is, however, beyond the capabilities of most laboratory technicians. In competent hands, it will, in 90% of cases, yield a diagnosis within an hour after the reception of the specimen. The diagnosis of an acute dysentery of either the bacillary or amoebic type, almost invariably can be made in a few minutes. The same may be said of the general run of non-inflammatory cases — the simple diarrhoeas. Therefore, it becomes possible to start specific treatment within an hour or two after the patient has reported himself ill.

No better corroboration of the above can be found than the statement of a British army medical officer writing from the Middle East Forces during World War II. He says: "We have given up examining stools of dysentery cases bacteriologically — all necessary information can be obtained from microscopic examination," (4).

In our work in the camps, dependence was placed solely on microscopical diagnosis. Bacteriological methods were not purposely excluded, but it was realized in the beginning, that it would be impossible to obtain, much less use, bacteriological apparatus and reagents. Events proved this to be true.

As a result of the employment of microscopical methods in the camps, we are now able to define the old terms "jail diarrhoea" and "asylum diarrhoea," and resolve the congeries into its components. It is now evident that "jail diarrhoea" is nothing more than a concentration and intensification of what might be termed community diarrhoea. All its components may be found the world over, in any community. The proportions in which the various components exist in a given place, vary in harmony with local conditions. They spread over a larger area and, hence, are not so spectacular. These conditions are not peculiar to the tropics: they are cosmopolitan. In the course of studies made by me since my return to this country, to be published later, I have found examples of every condition that was encountered in the prison camps. The net result of our camp studies is that a pattern

is now set for dealing with the problem presented by diarrhoeal disorders in the populations of war- and famine-stricken countries, to say nothing of communities in general. No longer is there any excuse for dealing with them in the old, haphazard way. In defining the picture as a whole, we indicate the means whereby this complex situation can be brought under control, even under the limited facilities and adverse conditions of the enemy prison camp. Manifestly, the control becomes easier in well-appointed communities provided the primary elements are distinguished from one another. Let us now resolve this symptom-complex group known as the diarrhoeal disorders into its components (Table I).

TABLE I

Grouping of the Diarrhoeal Symptom-Complexes

Diarrhoeal Disorders	Inflammatory (The Colites)	Dysentery: Bacillary. Salmonella. Protozoal. Helminthal. Chronic colitis: Post-dysenteric. Non-dysenteric.
	Non-inflammatory (Irritative)	Diarrhoeas: Fatty, Primary. Secondary Specific Fermentative, Primary. Secondary. Exfoliative catarrh. "Mucous colitis." Putrefactive, Secondary enterocolitis. Food intoxications (Salmonella etc.). Intestinal allergy. Gastro-enteritis.

I am showing (Chart A) the quantitative distribution of these conditions as they occurred in the

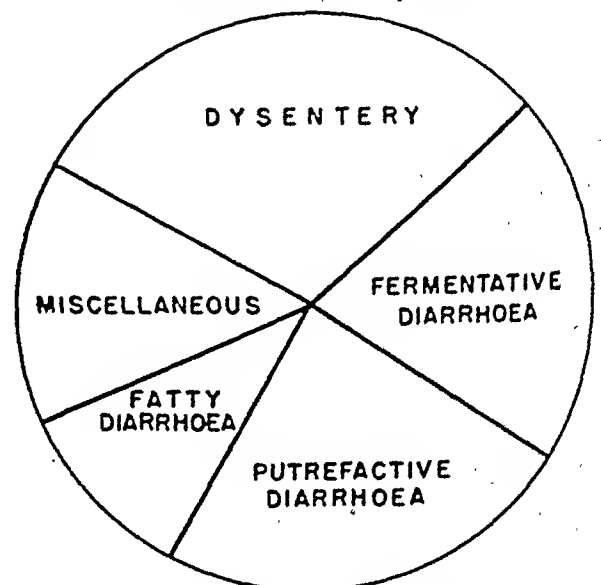


Chart A — Quantitative distribution of diarrhoeal disorders in Baguio Prison Camp, 1942-1943.

Baguio camp during the first eighteen months of the war. The non-inflammatory conditions — the diarrhoeas — are seen to greatly outnumber the dysenteric and other inflammatory processes. This is the state of affairs that usually is disclosed when surveys are conducted by qualified men. The tendency of unskilled men is to record many non-dysenteric cases as dysenteries if the stools are very mucoid as they often are.

With this background, we may now consider the basic principles upon which rest the microscopical diagnosis and management of intestinal disorders. They represent the crystallization of nearly thirty years of investigation and application during which the author has studied tens of thousands of stools passed in the course of all these types of bowel disorder. Much of this work was done under control by highly competent bacteriologists. Finally, it was critically reviewed in the proving ground of the prison camps. There it was possible daily to observe a large number of patients from the hour of the onset of their symptoms, through the acute stage and into the later developments of secondary involvement, recurrence of the primary condition, intercurrent complication and final subsidence of symptoms. These principles, which might even be called axioms, run as follows:

1. The diarrhoeal disorders — inflammatory and non-inflammatory — are symptom-complexes, not diseases.

2 The diagnoses are etiological — not clinical.

3. Treatment is based on a strict differential diagnosis in all cases.

4. The proper management of cases involves sustained microscopical supervision during the course of the illness and at intervals thereafter. The initial diagnosis is only part of the procedure. A conscientious follow-up is essential if the best results are to be attained. In the inflammatory conditions, it is the sequelae that contribute the most lasting mischief. In instances this is true of the non-inflammatory conditions. Acute bowel disturbances of all kinds are prone to develop secondary complications or recurrence of the acute phase. With vigilance, these may be checked in their incipience and further extension prevented.

5. Any material that is irritating to the intestinal mucosa — poisons, drugs or bacteria, causes an increased flow of blood, hypersecretion of the mucous membrane and varying amounts of oedema of the interglandular tissue. In the infectious lesions, the hyperaemia becomes more intense and exudate fills the tissue and appears on the surface of the mucosa.

In this paper we are dealing with the acute inflammatory processes — in other words, with the dysenteries or acute colites in the strict sense. This leads us to our next axiom:

6. Diagnosis of the inflammatory processes is made by study of the exudate derived from the bowel wall

and blood stream. This exudate corresponds to the histopathology of the process, in that it contains the cellular elements that are characteristic of it.

Infections with bacilli of the *Shigella* group produce the most intense inflammatory reactions in intestinal pathology. Once this cellular picture becomes fixed in the mind of the microscopist, he cannot mistake it for anything else. So striking is it, that it is useful to employ it as a basis for the interpretation of other exudates. Other inflammatory exudates from the bowel are of a simple purulent type. The features that distinguish the exudate of bacillary dysentery from other inflammatory exudates are characteristic of that condition alone. Their absence from pus emanating from the intestine, excludes bacillary dysentery from the diagnosis just as truly as does their presence signify a dysentery of the bacillary type.

The bulk of the bacillary exudate is, of course, made up of polymorphonuclear leucocytes. The specific characters of the exudate are to be found in the heavy content of phagocytic endothelial macrophages, and in the marked toxic necrotic changes in all cells. The necrosis is of the colliquative type, simultaneously involving all parts of the cell. Karyolysis is extreme and destruction of the cytoplasm often proceeds to a degree where nothing is left but the cell periplast containing a few granules, the product of cell lysis. Such cells are called ghost cells and they may be found in every exudate of bacillary dysentery; they appear in no other intestinal exudate. Changes in the neutrophile leucocytes also are striking. The nuclear lobes become resolved to rings, annular degeneration; the cytoplasm shows vacuolation and fatty degeneration. The exudate, as a whole, is made up of elements derived from both the bowel wall and the blood stream.

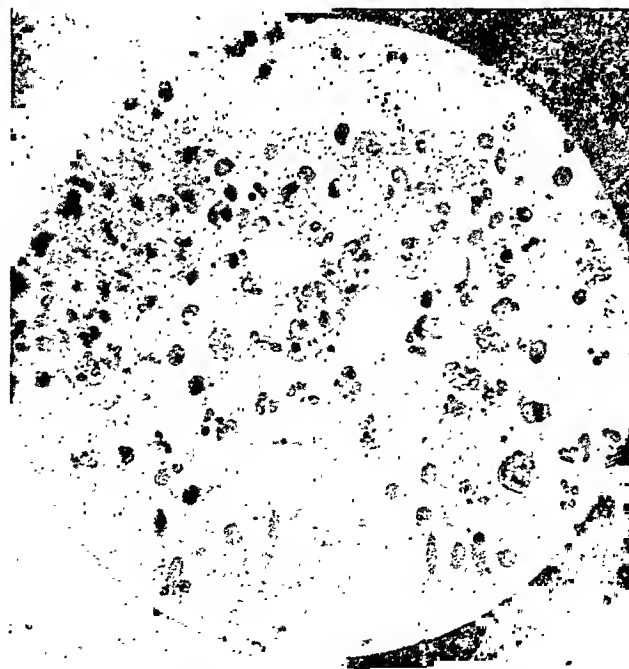


Figure 1 — Exudate of bacillary dysentery showing macrophages and other cellular structures, and evidence of cell necrosis.

Lymphocytes and large mononuclears are present in considerable number and one encounters plasma cells. Early bacillary exudates usually show little macroscopic blood, but erythrocytes always are found in the microscopical preparations. I am showing a typical bacillary exudate (Fig. 1). It was photographed from a preparation made in Santo Tomas Camp.

BACILLARY DYSENTERY

As one might suspect, the greater number of our bacillary dysenteries ran the familiar course that has so often been described. Therefore, it would contribute nothing to discuss them here. I shall write only of those observations that appeared to yield something new or, at least, a point of departure for further study.

From beginning to end, bacillary dysentery was endemic in both Baguio and Manila camps. In Baguio, our clinic handled the entire population of the camp which averaged about 500 persons. At Santo Tomas, about 2300 persons or 62% of the camp population, registered at our clinic. Of this total of about 2800 internees, diagnoses of primary or recurrent bacillary dysentery were made in 933 instances. The incidence of bacillary dysentery in our groups in both camps, was remarkably uniform, as is shown by Table II.

TABLE II

Incidence of Bacillary Dysentery in Baguio and Manila.

	Primary	Recurrent	Total	Percent of Registrants
Baguio	131	51	182	36.4
Manila	571	180	751	34.4

There were two well-defined epidemics in Baguio during the eighteen months of my residence there. Each subsided within a few weeks under improved sanitary conditions. Between the two outbreaks, there was a long period during which only a very few cases developed. These appeared to be recurrences. Bacillary dysentery was constant in Santo Tomas. On my arrival there in August 1943, I found that diarrhoeal disorders had been extremely prevalent from the early days. The conditions had been so serious that the Japanese authorities had taken the camp medical staff to task. Many of the camp inmates had been severely ill and there had been some deaths. It developed that most of the patients had been treated under a blanket diagnosis of "enteritis" and there was nothing on the records to show the precise nature of their bowel disturbances. Few specific diagnoses had been made. However, the large number of persons suffering from post-dysenteric colitis who presented themselves at our clinic as soon as it was established, made it very evident that the incidence of bacillary dysentery in Santo Tomas had been high from the beginning.

There is little doubt that the bacillary dysenteries in the two camps all were of the paradysenteric type. Infections with *Shigella dysenteriae* are rare in the Philippines. In both camps, the short course of the dysenteries gave rise to doubt, on the part of some

of the camp physicians, that dysentery was present. This a common misapprehension that is born of the fact that the general practitioner seldom sees a case of dysentery until it is well established and the stools have become muco-purulent and bloody. Most of our primary diagnoses were made on stools that were still muco-feculent, and in which no gross blood could be seen. The short course our dysenteries ran was consequent upon early diagnosis and immediate treatment. I have found that many physicians are unwilling to start antidysenteric treatment unless the microscopist reports that the stool is bloody. As erythrocytes always are found in the exudate, this difficulty is easily overcome by the entirely true statement that blood is present.

It was deemed desirable to dispel this misapprehension. Accordingly, the Japanese Army Medical Corps was asked to make a bacteriological check. Rectal swabs were passed on seven patients ill with bacillary dysentery and immediately inoculated on culture media. Flexner organisms were recovered from five of these and the doubts were dispelled. At Santo Tomas, the Japanese medical officers took cultures from a number of dysenteric stools. They reported all to be negative. Investigation showed not only were the stools stale, all the patients had been under treatment with sulfaguanidine. Obviously, these results were valueless. Those were the only bacteriological studies we had. Clinically, the cases ran the usual mild to moderately severe course characteristic of paradysenteric infections. There were few fulminant cases and all occurred in patients who either had been sick for several days before turning themselves into the clinic, or who were in an advanced state of malnutrition and exhaustion.

MASKED DYSENTERY

An interesting feature of the acute bacillary dysenteries was afforded by the rather high incidence of cases of "masked dysentery" that developed among the inmates of the camps. This is a condition, the diagnosis of which often is missed. Accordingly, it probably is more common than the general run of physicians would believe. The high incidence of this condition in our clinics may be attributed partly to the fact that the internees had been early impressed with the importance of reporting to the Intestinal Clinic immediately upon the development of any bowel symptoms. Moreover, there scarcely was a normal intestine in the camps. The state of chronic intestinal irritation from which most of the inmates of the camps suffered as a result of improper diet and the ingestion of irritating substances, may have been a predisposing cause.

This condition may be compared to what is spoken of as *cholera sicca*. Pain, sometimes very severe, suddenly develops somewhere along the course of the colon, the temperature rapidly mounts and marked symptoms of toxæmia appear and quickly deepen. There are no bowel movements and the patient has no impulse to defecate. Usually, the physician thinks

first of some surgical condition, but the picture is not clear. Within a few hours, the patient becomes extremely toxic and still the bowels do not move. I have seen instances, before the war, in which the patient died without passing a single bowel movement, but lesions of bacillary dysentery were found at autopsy. Rarely, perhaps after the lapse of several days, the bowel may move. The first faecal movement is succeeded by the passage of the typical purulent exudate of bacillary dysentery. The patient may then pull through on the application of intensive anti-dysenteric treatment. If the bowels do not move, the prognosis is grave. Death may come with shocking suddenness.

Suggestions that the condition may be bacillary dysentery usually are received with incredulity by the attending physician, which is not surprising. However, in most instances, it is possible to clear the picture by administering saline enemata. The microscopist must then camp down on the job. The first movement probably will be composed of the faecal contents of the lower bowel. It should be thoroughly searched for flecks of mucus which are likely to be present. These will yield the evidence upon which a diagnosis of dysentery can be made. If the case is one of dysentery, the stools will become frankly dysenteric within an hour or two. The prognosis usually bears a close relation to the time that has elapsed between the onset of symptoms and the diagnosis. By the time the bowels have moved, the patient usually is very ill and time has become a vital factor if he is to survive. The thirty-six or more hours required to make a bacteriological diagnosis may determine a fatal issue. Cytodiagnosis may be made from the first stool passed or, at the latest, within an hour or two. The lesson is obvious. I never have seen this condition develop in amoebiasis.

RECURRENT BACILLARY DYSENTERY

I use the term recurrent bacillary dysentery, because, in my opinion, it defines the condition more accurately than the frequently used term, chronic bacillary dysentery. The chronic colitis that often follows a bacillary dysentery, is caused by bacteria other than the dysentery bacillus — it is not a continuation of that infection. Recurrent bacillary dysentery definitely is caused by dysentery bacilli. Its manifestations are abruptly intermittent and are superimposed on the exudate of the chronic secondary colitis.

The plans for the prison camp studies included an inquiry into the frequency of recurrent bacillary dysentery, the number of recurrences of a given case that may occur and the period following the primary attack within which it is most likely to develop. It would be hard to find conditions more favorable to such a study as those afforded by the camps. The prime essential for such a study is a controlled stationary population, in which it is possible to segregate groups of persons in whom a diagnosis of primary bacillary dysentery can be made beyond a reasonable doubt. Such subjects must then be held under con-

stant observation and subjected to almost daily clinical and microscopical study for a period of at least a year. During this period, the primary access may be seen to develop, run its course, subside and finally become lost in the pathology of post-dysenteric colitis. At intervals, the cellular picture of colitis may revert to that of acute dysentery and the observer knows a recurrence is developing. Treatment against the acute exacerbation can immediately be instituted and extension prevented. Often the recurrence can be aborted in a few hours. Usually, then, the chronic process again becomes dominant in the microscopical picture. The process may thus continue *ad infinitum*, and may be recorded as it runs.

Observations on several hundred cases of bacillary dysentery in the prison camps, have shown that recurrence may be expected in about one-third of primary bacillary dysenteries. I have culled from these records, 231 cases in which the primary nature of the first attack was established beyond reasonable doubt and in which new infection could be excluded with equal confidence. Fifty-one of these patients were studied in the Baguio camp and 180 in Santo Tomas. All were under observation for twelve months. Their stools were examined daily for the first two months and, thereafter, at intervals of not more than three days. The number of recurrent attacks these patients sustained are recorded in Chart B, in percentage for each camp.

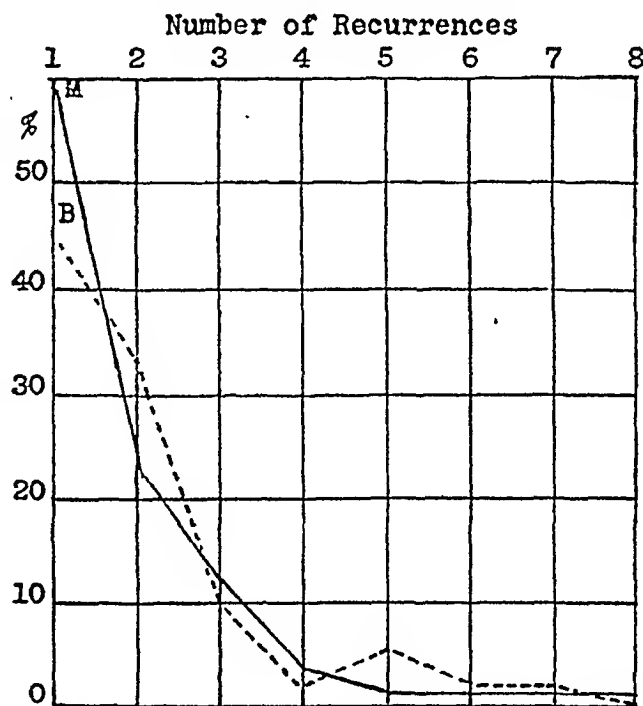


Chart B — Number of recurrences of bacillary dysentery in Prison Camps in Manila (M) and Baguio (B).

It will be seen that by far the greater number of these patients suffered no more than two recurrences. After that, the curve falls rapidly. The greatest number of recurrent attacks suffered by any individual patient, was eight. The number of recurrences in most

instances was not more than three within the twelve-month period of observation.

The observations in Baguio were made during the first eighteen months of imprisonment before depletion of vitality had become marked. Those in Manila were made during the last eighteen months at which time the vitality and resistance of the prisoners had been seriously undermined, and yet the difference is not great. Why is this?

Summarizing our findings I find that in Baguio 78.4% of our group sustained a maximum of two recurrences. In Manila the figure was 83.2%. This leads us to believe that approximately 80% of patients will have no more than two recurrences.

In Baguio, 74.9% of our recurrences took place within the first three months following the primary attack. In Manila, the figure was 65.2% which indicates that 70% of recurrences are likely to take place within three months of the initial attack. It therefore, may be suspected that acute attacks developing after the third month may be new, exogenous, infections. In short, one gains the impression that most primary bacillary infections wear themselves out in that time.

I cannot go into details here; I have discussed them elsewhere (5). I incline to the view that, most, if not all, recurrent bacillary dysenteries have their origin in the rupture of the mucous retention cysts that often form in the course of the healing of bacillary lesions. Viable dysentery bacilli have been recovered from these cysts five or more years after the initial attack.

The greater number of recurrences in the camps, developed in the course of a chronic post-dysenteric colitis, but a sufficient number of them occurred after the colitis had subsided, to indicate to us that retention cysts can persist in an otherwise healed gut. The epithelial walls that separate the interior of these cysts from the lumen of the bowel are very thin, sometimes consisting of only one or two layers of epithelial cells (Fig. 3 A). The blood supply of this membrane is very scant and doubtless there often is necrosis leading to spontaneous rupture of the cyst and the liberation of its contents into the intestine. Comparatively slight trauma, such as might be caused by hard faeces, excessive peristalsis or extreme distention of the gut are likely to bring about the same result. Our observations in the camps led us to the belief that most of our bacillary recurrences were precipitated by the extreme distention and peristalsis of intercurrent fermentative diarrhoeas.

In patients with a post-bacillary colitis, who are under constant observation, one may detect the cell picture of acute dysentery in the post-dysenteric exudate while the recurrent process is still localized in the mucosal area adjacent to the ruptured cyst. Prompt treatment at that time usually will abort the recurrence. It always is possible, microscopically, to distinguish between a true recurrence and an intensification of the chronic post-dysenteric colitis.

CONCURRENT BACILLARY AND AMOEBIC DYSENTERY

Only twenty-one cases of *Endamoeba histolytica* infection were detected in our clinics. Twelve of these developed acute dysenteric symptoms. The other nine remained carriers throughout the period of observation. It was possible to record data on twelve carriers of *E. histolytica* in whom bacillary dysentery later developed. Trophozoites of the amoeba appeared in six during the course of the bacillary dysentery; six remained carriers. The active amoebae did not appear in the stools until the bacillary access had been in progress for three or more days. The question naturally arises as to why trophozoites appeared in six of the cases and why they failed to appear in the other six. Speculation on this point necessitates a brief review of the comparative pathology of amoebiasis and bacillary dysentery.

In the carrier stage of amoebiasis the habitat of the amoebae is the submucosa. There, the parasites nourish themselves on lysed connective tissue. The destruction spreads radially and cavities are formed by this extension and by the coalescence of adjoining lesions. These cavities contain lysed products of the proteolytic action of the amoebae, cell detritus and amoebae. There is no inflammatory reaction and the mucosa overlying the submucosal lesions may remain intact over long periods of time during which only the precystic and encysted forms of the amoebae appear in the stools. If the bridge formed by the mucosa and muscularis mucosae breaks down, active tissue-dwelling forms (trophozoites) of the amoebae

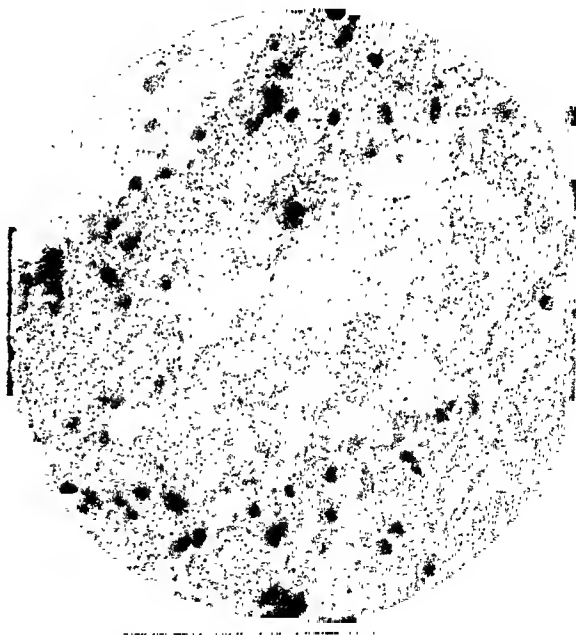


Figure 2 — Exudate of amoebic dysentery with early secondary colitis. Note the feculent, bacteria-laden stool and absence of cell necrosis and endothelial reaction. Two trophozoites of *Endamoeba histolytica* are in the center of the figure.

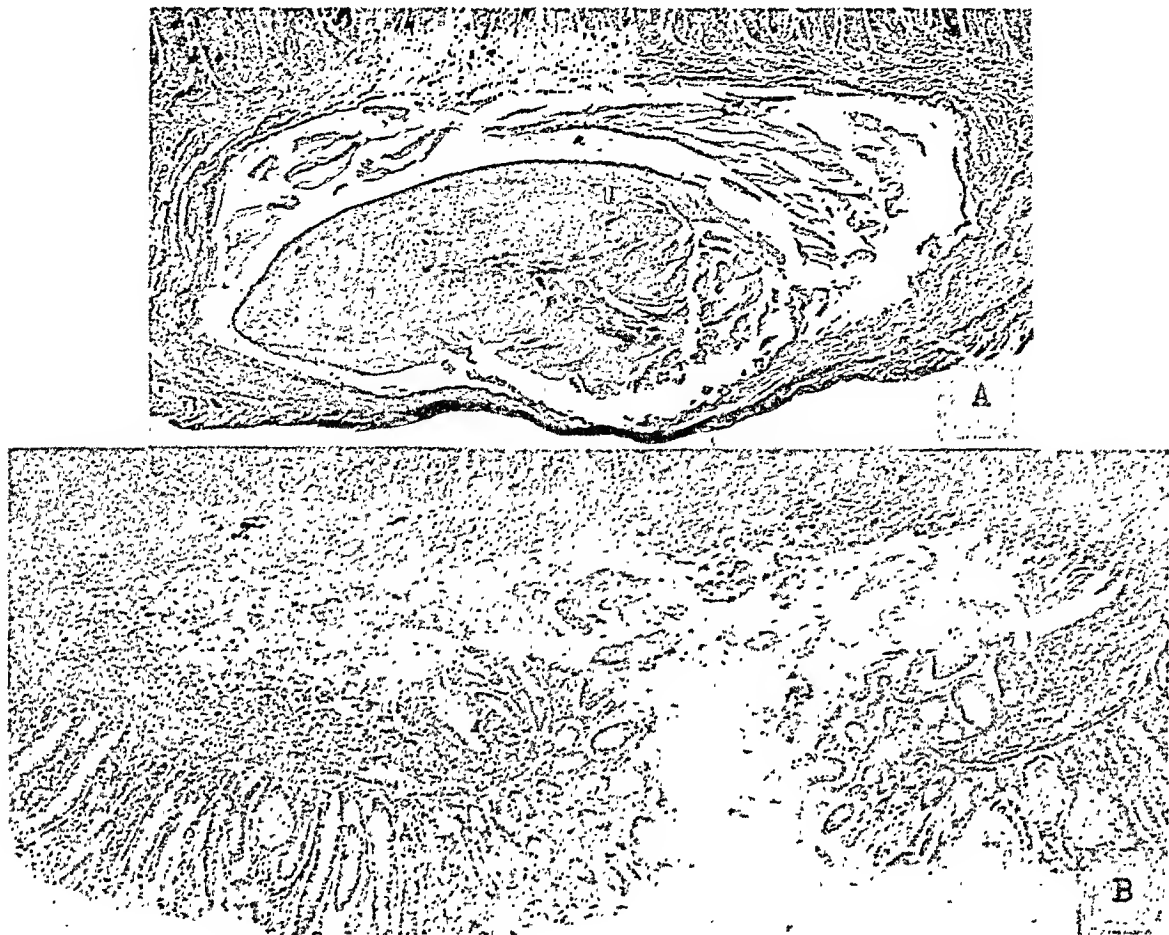


Figure 3 — Section of bowel wall showing mucous retention cyst (A). The section through an amoebic ulcer (B), shows the typical "bottle neck" structure. Note the muscularis has walled off the infection and that the mu-

cosa and muscularis mucosae are intact except at the neck of the "bottle." Destruction is limited to the submucosa. Army Institute of Pathology, Neg. Nos. 77481 (A) and 80676 (B).

appear in the stools, bacteria gain access to the unprotected cellular structures and inflammation ensues. In the beginning, the leucocytic reaction is slight (Fig. 2), but it grows rapidly in volume and the simple proteolytic process becomes overshadowed by the secondary inflammatory reaction. In uncomplicated amoebic dysentery, there is not the cell necrosis that is such a prominent feature of the bacillary exudate. However, unlike bacillary dysentery, the stools in early amoebic dysentery are likely to be haemorrhagic because of the deeper involvement of the amoebic process. If the reader will compare the figures of the retention cyst and the amoebic bottle-neck ulcer (Fig. 3 A, B), he will likely conclude that the same influences that bring about the rupture of a mucous retention cyst in bacillary dysentery, may break down the bottle-neck of an amoebic ulcer.

lus without, and the amoebae within it, probably is sufficient to break down the barrier with resulting

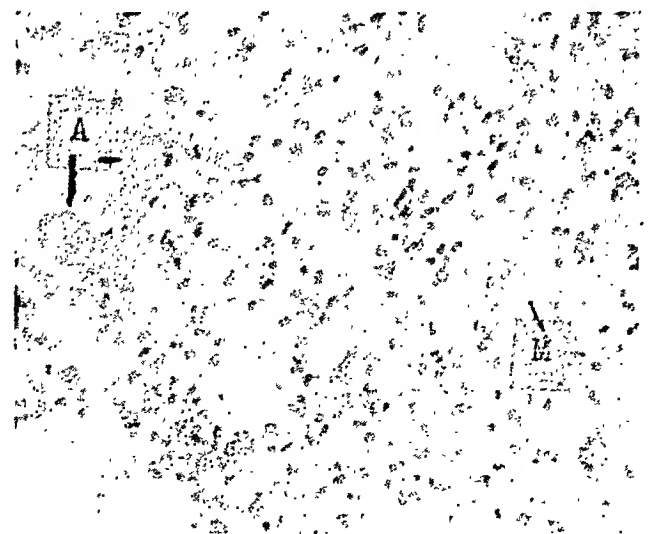


Figure 4 — Exudate of concurrent bacillary and amoebic dysentery showing two trophozoites of *Endamoeba histolytica* (A) and a necrotic macrophage (M). The cell picture is typically bacillary and evidence of toxic necrosis is marked.

In bacillary dysentery, the mucosa is first involved and in mild cases the destruction does not proceed past the muscularis mucosae. This structure seems to afford a fairly resistant barrier to the entrance of the dysentery bacilli and the exit of the amoebae. If a bacillary ulcer forms on the same area of the bowel within which lies an amoebic cavity, the combined action on the muscularis mucosae, of the dysentery bacil-

appearance of trophozoites of the amoeba in the stools. We then have concurrent bacillary and amoebic dysentery. The cellular picture will be that of an acute bacillary dysentery with amoebae moving about in the exudate (Fig. 4). One should make sure that the amoebae are *E. histolytica* and not *E. coli* before starting anti-amoebic treatment. One often sees trophozoites of the harmless *E. coli* in bacillary stools. Inexperienced microscopists are apt to stamp such cases amoebic dysentery.

The above would seem to offer an explanation of amoebic dysentery supervening upon bacillary dysentery. It also may explain why trophozoites appear in some carriers of *E. histolytica* during the course of a bacillary dysentery and not in others. In the latter

event there probably has been no juxtaposition of amoebic and bacillary lesions.

Obviously, twenty-one cases of amoebiasis provides no adequate basis for drawing sweeping conclusions regarding the factors that bring about concurrent bacillary and amoebic dysentery. However, these speculations afforded a point of departure for future work. Pathologists should be on the alert for fatal cases of concomitant bacillary and amoebic dysentery. Study of the distribution of bacillary and amoebic lesions with special reference to areas in which both types of lesions are to be found, should be very instructive.

In the next paper I shall discuss the matter of post-dysenteric and non-dysenteric colitis from the viewpoint of diagnosis, and the influence of treatment on the incidence of secondary colitis.

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X-Ray Examination of the Vermiform Appendix

By

A. J. DELARIO, M.D.

PATERSON, N. J.

THE TRUE VERMIFORM APPENDIX is found primarily in man and higher apes. In some lower animals an extended pouch of the cecum is present resembling an appendix. This large appendiceal pouch can readily empty itself and thus rarely becomes diseased. But in man, the lumen of the appendix is so long and narrow that stasis of various degrees is the rule. Along with trauma due to foreign bodies, worms and fecaliths, this stasis with accompanying products of fermentation and putrefaction, subjects the mucous membrane of the appendix to a great deal of irritation and infection. The resultant inflammatory lesions are very common. Probably all of us at sometime in our life have some involvement of the appendix and a great many have to have their appendices removed. Appendectomy is probably the most common of all operations.

In the majority of cases with appendiceal disease, the surgeons need very little help from the roentgenologist. This is especially true in acute appendicitis. However, there is still need for improvement in the diagnosis of acute appendicitis.

In about 10 to 15 per cent of cases with clinical symptoms of appendicitis, at operation a normal appendix is found. Rosenberg (28), in 100 cases operated on for acute appendicitis and in whom a normal appendix was found, discovered in about half of the cases some other pathology, acute mesenteric adenitis in 17; acute ovarian conditions in 16, such as rupture of Graafian follicle in 3, rupture of Graafian follicle followed by intraperitoneal bleeding in 6, hemorrhage in corpus luteum cyst in 4, pelvic tube disease in 3; acute right pyelonephritis in 2; cholelithiasis in 2; acute gastro-enteritis in 5; acute regional ileitis in 2; ileo-cecal tuberculosis in 1; pericecal granuloma in 1; acute purulent Meckel's diverticulitis in 1; carcinoma of the appendix with mucocoele in 1; infarct of the appendix epiploica of the cecum in 1; small intestinal obstruction with infarct in 1; acute right epididymo-orchitis in 1; and acute catarrhal jaundice (jaundice developing 4 days postoperatively) in another. In the remaining cases he found no pathology at all.

X-ray examination of the gastro-intestinal tract would have lead to the correct diagnosis in some of these cases and the showing of a normal appendix would have prevented operation in others.

Acute right lower quadrant pain occurs at times with recognizable and nonrecognizable respiratory infections. Tonsillitis is occasionally the precursor to appendiceal pain. Appendiceal pain is occasionally present in the common contagious diseases. The cause for the lower right quadrant pain in the above conditions may be due to their tendency to cause generalized lymphoid overgrowth and especially of the appendix which many consider essentially a lymph gland and which has been called the abdominal tonsil. This lymphoid hyperplasia is most common in male children between the ages of 1 and 10, Hwang and Krumbhaar (16). These pseudo-appendicitis cases have symptoms of nausea, vomiting and localized pain in the lower right quadrant. The leucocyte count is not apt to be high. Occasionally the lymphoid hyperplasia may be sufficient to block the appendiceal lumen causing more

severe appendiceal changes and surgical removal must be undertaken. Goodman and Silverman, (15). Many chest conditions by involving the right lower pleural wall may give pain in the lower right quadrant, the pain referred along the lower right intercostal nerves.

In these cases also either ruling out by X-ray examination, chest conditions etc. that might cause lower right quadrant pain, or demonstrating a normal filling appendix will help the surgeon in arriving at the correct diagnosis of acute appendicitis.

It is in the subacute and chronic cases of so called appendicitis that the X-ray examination can be of greater benefit. For it is in this group that results of appendectomy are poorest. Some have found no improvement in as high as 70 per cent of cases (Coffey) and others have found no improvement in as low as 24 per cent of cases (Presbyterian Hospital N. Y. C., 1922), Gomez (14), Connell (6), and Gibson (13), say that 40 per cent of 638 patients show no improvement after operation. If routine X-ray examination were done on these cases either the appendix would show some pathology in the cases that would improve with appendectomy; or good appendiceal function, or some other disease would be found in the cases that would not improve by appendectomy.

It must be stressed, however, at this point, that regardless of how pathological the appendix may appear by the X-ray examination, it does not mean that surgical intervention is immediately required or that the appendix is even giving symptoms or signs. The X-ray findings may be residual findings due to pathology in the past. But in conjunction with the history, physical examination and other laboratory procedures, these X-ray findings may be important.

The appendix X-ray examination will reveal many facts that can't be obtained by the clinical examination such as anomalies, anatomical type, the shape, the position and size of the appendix; its mobility, whether kinking as the result of adhesions or bands is present; tenderness on palpation; peristaltic movements and segmentation; the presence of foreign bodies, concretions, fecaliths or appendiceal stones, its filling and emptying. A knowledge of these facts helps one to determine whether the appendix is pathological.

Inflammatory lesions of the appendix cause reflex changes in other organs some of which can be studied by X-ray. For instance, spasm might be seen in the stomach, small and large intestine especially of the cecum. Appendiceal abscess may also cause pressure defects upon the cecum and lower ileum. It may produce changes in the right psoas muscle outline and in the curvature of the lumbar vertebra.

Diverticula of the appendix can be visualized. Sometimes intussusception can be diagnosed. Tumors of the appendix can occasionally be seen.

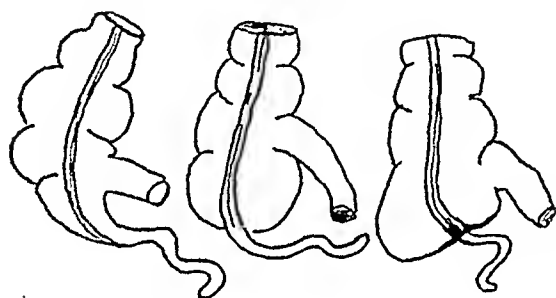
ANOMALIES OF THE APPENDIX

The appendix may be absent but this is a very rare occurrence. Double appendices have occasionally been recorded. Cave (4) describes various duplex appendices as follows: (1) A single cecum with one appendix exhibiting partial duplicity, a double barreled appendix; (2) A single cecum with complete duplicity of the appendix; (3) Duplicity of the appendix and duplicity of the cecum, each cecum having its own appendix. Cave believes that the non-pathological diverticula of the appendix is an attempted duplicity of the appendix.

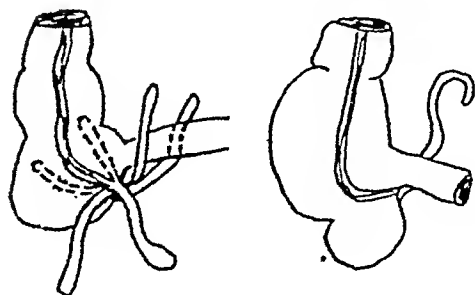
ANATOMICAL VARIATIONS IN FORM AND POSITION OF THE APPENDIX

These variations depend to a great extent upon variations in form and position of the cecum. Three variations in the form of the cecum are commonly described.

1. The fetal type is conical in shape with the inferior end gradually passing into the appendix. The three muscular bands which meet at the appendix are nearly at equal distances apart. The appendix usually points downwardly. See Figure 1 A.



A. B. C.



D. E.

Figure 1. — Line drawing of anatomical types of cecum and appendix. A. Fetal type. B. Infantile type. C. Adult type. D. Adult type showing positions appendix can assume in relation to the cecum and ileum. E. Adult type type showing the appendix very close to the ileo-cecal junction.

2. The infantile form is more quadrilateral in shape than the last. The passage from the cecum to the appendix is more abrupt. The three bands retain their relative position; the appendix appears between two bulging sacculi, instead of at the summit of a cone. The appendix usually points downwardly. See Figure 1 B.

3. In the adult type, that part of the cecum lying to the right side of the anterior band grows out of proportion to that part to the left of the band. The anterior wall becomes more developed than the posterior, so that the apex with the appendix is turned so much to the left and posteriorly that it nearly meets the ileocecal junction. A false apex is formed by the highly developed part to the right of the anterior band. The appendix is usually to the left or behind the cecum. See Figure 1 C. It may, however, be found in any of the positions shown in figure 1 D. It may point downward, it may lie behind the cecum, in front of or behind the ileum. This is the usual cecum and appendix found in 90 per cent of adults. Occasionally, the development of the part to the right of the anterior band is excessive, while the segment to the left of the band has atrophied. In this form the anterior band runs to the inferior angle of junction of the ileum with the cecum. The root of the appendix is posterior to that angle. There is no trace of the original apex, and the appendix appears to spring almost from the ileocecal junction and lies behind or in front of the ileum. See figure 1 E.

The position of the cecum and appendix also depends upon the degree of rotation of the intestines during fetal life. During approximately the fourth month of gestation, the cecum leaves its position on the left side of the abdomen, ascends and with its mesenteric attachment as a handle rotates in the form of a partly open fan into the right iliac fossa. However, ascent and rotation may stop at any point. Thus the appendix may be found anywhere along the course described by the cecum. It may be found on the left side of the abdomen and along the line of the transverse and ascending colon to the right iliac fossa.

During the descent of the cecum and appendix, the appendix occasionally becomes attached to the posterior parietal peritoneum especially if the meso-appendix is short, and in the course of absorption of the posterior investment of the right colon, comes to lie outside of the peritoneal cavity. It is then known as a retroperitoneal appendix. It usually lies behind the ascending colon where it is referred to as a retro-colic appendix. A retro-colic appendix is almost always retroperitoneal.

In the past these retro-colic or retroperitoneal appendices were referred to as retro-cecal. In the majority of cases, however, the appendix is found behind the cecum and is covered with peritoneum. About 70 per cent of all appendices are retro-cecal and in only 7 per cent do they become retro-colic as well and usually become retroperitoneal in so doing.

The retroperitoneal appendix is peculiarly susceptible to acute inflammation. The incidence of acute inflammation in retroperitoneal appendices is about five times as frequent as in the usual appendix. Busher (3). Small (31) states that a retroperitoneal appendix is liable to disease because it is cut off from the direct superior mesenteric circulation. MacLeod (20) states that a retroperitoneal position closely related to the right ureter favors obstruction of the appendix at the point where the appendix bends toward its junction with the cecum and that this renders it liable to disease. However, it is more probable that the fixed position of the appendix prevents proper muscular contraction and proper emptying; the ensuing stasis starting the train of events leading to inflammation.

The X-ray visualization of the appendix is important in affections of the retroperitoneal appendix because

the usual symptoms of appendicitis are not present. The onset of epigastric pain followed by nausea and vomiting is frequently present but the later localized pain over McBurney's point is usually absent. The tender point is more apt to be in the loin above the crest of the ileum. Muscular spasm of the anterior abdominal wall is usually not present. Irritation and contraction of the psoas muscle is apt to be present with flexation of the right thigh upon the abdomen.

A retroperitoneal or retro-colic appendix even if not visualized can be suspected when in the X-ray examination, the ileum can be seen projecting from the cecum at about its apex instead of medially and to the left. The terminal ileum is not movable, not only because the cecum is more or less fixed but also because of the presence of Lane's kinks (a band stretching from the terminal ileum to the pelvis peritoneum). Lane's kinks are present in about 90 per cent of retro-colic appendices, Spivak (33). When the appendix is visualized it will be found extending up behind the cecum and ascending colon more to the right and to its lateral edge.

The position of the cecum and the appendix depends not only upon the degree of intestinal rotation but also upon the length of the proximal colon, the length of its mesentery and to what degree it becomes adherent to the posterior parietal wall. An appendix may be on the left side of the abdomen not only because of non-rotation, but also because the proximal colon and its mesentery is redundant, not attached to the posterior parietal wall and thus can extend over to the left side of the abdomen. It may be found under the liver or in a right inguinal hernia sac. Occasionally in cases of right sided diaphragmatic hernias, the appendix has been found in the right pleural cavity. The appendix is usually low in hyposthenic and high in hypersthenic individuals.

The position of the appendix modified by extrinsic and intrinsic pathology. The position of the appendix also depends upon the presence of pathology in adjacent organs and in the appendix itself. The cecum and the appendix may be displaced upward by tumor masses in the pelvic organs such as fibroid uteri, ovarian cysts, and tubal infection. It may be displaced medially by an ectopic kidney. It may be displaced downwardly by lesions of the gall bladder, liver and kidney. It may be displaced laterally by retroperitoneal masses, mesenteric cysts, etc. Occasionally the appendix may be bound down by adhesions from pathological conditions in surrounding organs. When the appendix is diseased it often attaches to adjacent organs in unusual positions.

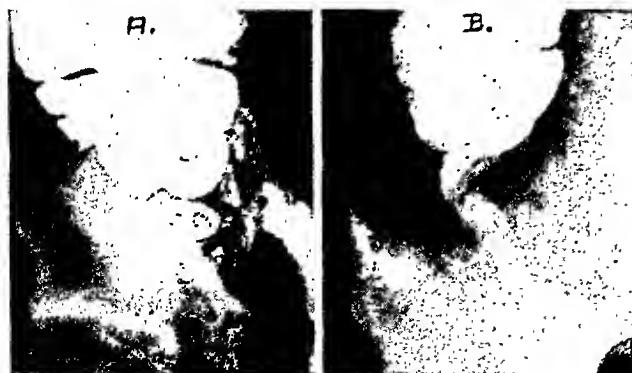


Figure 2. — X-ray reproductions of anatomical type of cecum and appendix. A. X-ray examination showing infantile type of cecum with a short, thin appendix. B. Infantile type of cecum with a short thick appendix.

Thus a pathological appendix may give symptoms and signs almost any place in the abdomen and may simulate many other conditions. Pain and tenderness over McBurney's point doesn't necessarily mean appendicitis nor does pain and tenderness in other parts of the abdomen necessarily rule out appendicitis.

SIZE OF APPENDIX

The average length of the appendix is 8 to 10 centimeters. It has been found as long as 20 to 25 centimeters and as short as one-half a centimeter. The appendix is longer in the young than in the old individual and about 1/2 to 1 centimeter longer in the male than in the female. The appendix is relatively to the rest of the large intestine larger in the child at birth than in the adult, the proportion being 1 to 16 or 17 at birth, and 1 to 19 or 20 in adult. The appendix attains its greatest length and diameter during adult and middle age and atrophies slowly after this time, (7). The long appendix may be normal, but it is usually a potential source of pathology. The short appendix may appear so because of obliteration of its distal end as a result of infection.

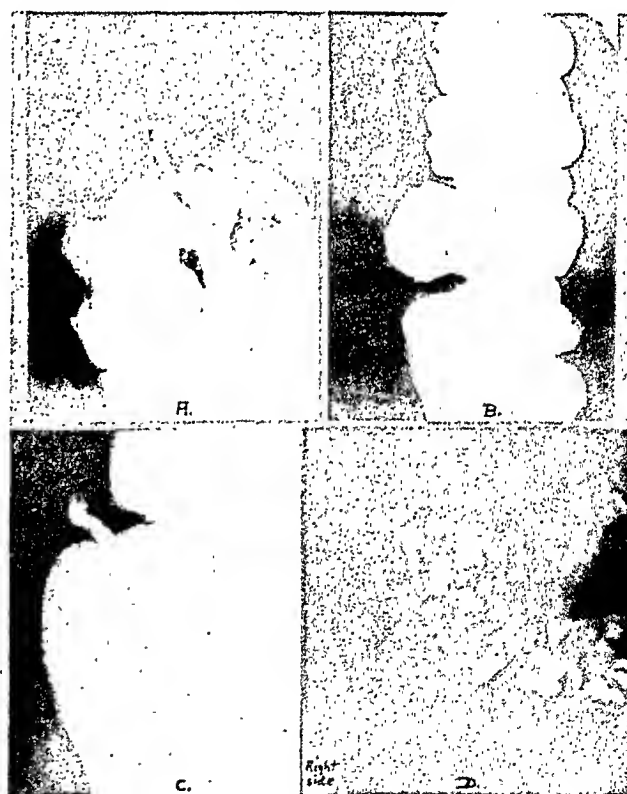


Figure 3. — Position of the appendix depending upon the degree of rotation of the cecum. Appendices in B. and C. have a greater tendency to become diseased. A. Showing appendix with fecaliths underneath the liver. B. Showing a retro-colic appendix with fecaliths most of which lies lateral to the ascending colon. C. Retro-colic appendix, the tip of which shows lateral to the ascending colon. D. Appendix with fecaliths in the left lower quadrant due to a redundant ascending colon with a long mesentery.

The caliber of the lumen of the appendix is generally wider at the base and narrows slightly towards the tip. It has a tendency to decrease in size with age.

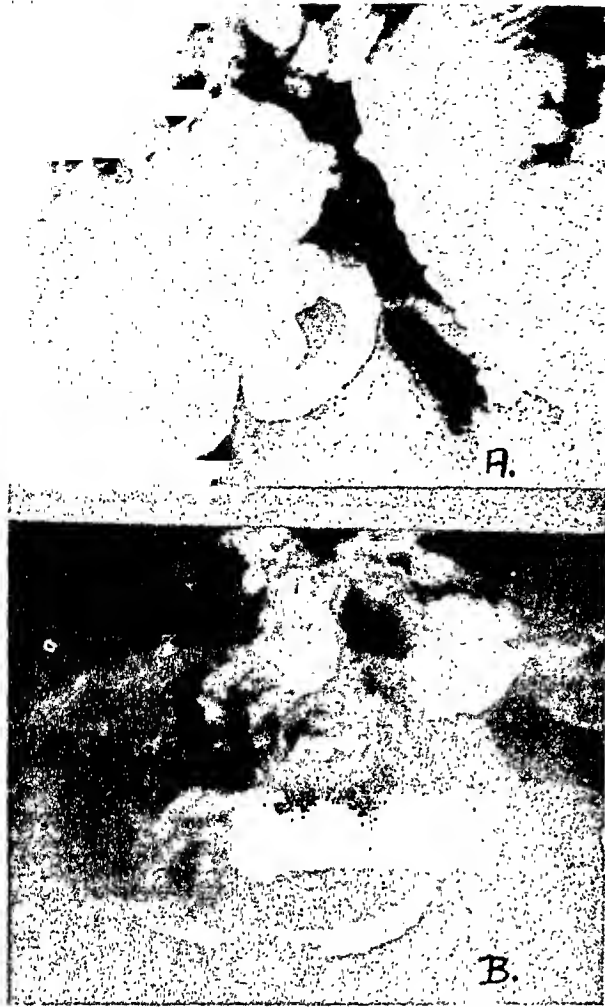


Figure 4. — Position of the appendix modified by pathology. A: Shows persistent kinking of the mid-appendix. At operation numerous adhesions were found about the appendix. B: The tip of the appendix is persistently fixed to the lateral aspect of the apex of cecum. At operation the appendix was found bound down by adhesions.

It is found partially occluded in 25 per cent of adults, and in 50 per cent of those over 60 years old coming to autopsy. It is totally occluded in 3 to 4 per cent, where it is converted into fibrous cord (7). It is probable that these changes are the result of appendiceal disease.

An irregular or filiform narrowing of the lumen indicates obliteration by diffuse thickening of its wall. Complete or partial dilatation and complete or partial constriction of the lumen is usually a sign of disease. The presence of areas of both dilatation and constriction in the same appendix is usually pathological. Clublike dilatation of the distal end is usually abnormal. Persistent irregularities and kinking of the lumen by adhesions or congenital bands are pathological. These changes in the size of the lumen should be persistent. It is not unusual for the lumen to appear narrow in one examination and to be wider later as more barium enters the appendix.

Mobility of the appendix, the presence of adhesions,

kinks, congenital bands and membranes. The normal appendix with exception of the retro-colic and retroperitoneal type is mobile and moves with the cecum. Under the fluoroscope the appendix may be moved freely. If it does not move freely the chances are it is bound down by scar tissue from present or past pathology or congenital bands.

The ileo-cecum is a frequent site for unusual peritoneal folds, congenital bands, and membranes. In addition to the mesentery of the appendix, there is the ileo-colic or anterior vascular fold containing the anterior branch of the ileo-colic artery. The ileo-cecal or the bloodless fold of Treves runs from the lower border of the ileum to the cecum. There is Lane's kink or band stretching between the terminal ileum and the pelvic peritoneum. Jackson's membrane spreads from the parietal peritoneum to the cecum and ascending colon, and is often adherent to the great omentum.

These congenital bands and membranes often run in families and render them liable to acute appendicitis which necessitates their removal. Down (9), reports in a family of 22, one man and his descendants of three generations that 16 acute appendices had to be removed. All at operation had an appendix sharply kinked at the base by a band of fibrous tissue which bound it to the outer side of the cecum.



Figure 5. — Unchanging size of the appendix denoting pathology. A. Persistently short, thin appendix, the distal end was obliterated by fibrosis. B. Persistently long, thin appendix which took more than a week to empty. C. Persistently long, thin appendix with bulbous end containing a fecalith. D. Appendix in which the proximal half is persistently constricted and the distal half dilated. All the above patients had a history of appendiceal pain, probably at times when it was difficult for the distal end of the appendix to empty itself through the narrow proximal end.

Nicholson (24) feels these congenital bands cause mechanical deformities of the appendix which are responsible for ill health, poor nutrition, poor development in children and ultimately lead to acute appendicitis.

Tenderness and muscular rigidity in appendiceal disease. The whole subject of pain, tenderness and muscular rigidity in appendiceal disease is not complicated in the vast majority of cases. The appendix like other abdominal organs has autonomic afferent nerves which are insensitive to tearing, cutting and clamping but are sensitive to distention. The somatic afferent nerves innervate the parietal peritoneum and the mesentery but not the serous coverings of the bowel itself. These are sensitive to tearing, cutting and clamping. According to Morley (23) in counterdistinction to segmental pain, tenderness, and muscular rigidity caused by nerve root pressure, appendiceal disease causes local pain, tenderness and muscular rigidity when the parietal peritoneum or the mesentery close to the appendix is involved.

This subject of pain, tenderness and rigidity becomes complicated when the subject of the left sided appendicitis is discussed. Pol (27) found in 46 cases of left sided appendicitis where situs inversus viscerum was present (total in 34 and partial in 12) in more than half the pain localized to the right side. Apparently the lower right quadrant pain, tenderness, and rigidity is just as severe and gripping in left sided appendicitis as it is in right sided appendicitis. It is difficult to explain this right sided pain, tenderness, and rigidity to right parietal peritoneum and mesenteric involvement since the appendix is on the left side.

Kuntz (18) believes that in cases of appendicitis in transposition of the viscera, referred phenomena ought to be localized on the right side for even though the viscera are transposed their nerve supply remains the same. This should be true for the visceral pain due to distention carried by the autonomic nerves. The left sided pain, tenderness and rigidity is probably due to parietal peritoneum or mesentery involvement and these impulses are carried by the somatic afferent nerves on the left side of the abdomen.

In summary it may be said that initial pain due to distention as the result of edema and inflammatory reaction of the appendix is carried by the unmyelinated autonomic afferent nerves and the pain will be felt in the lower right quadrant. This will be so in right sided appendices, in appendices situated anywhere as the result of a long, loose, ascending colon and cecum; or in excessively long appendix which might cross to the left of the midline; or in complete or incomplete transposition of the viscera. Tenderness and rigidity are phenomena due to local involvement of the parietal peritoneum and mesentery and will be elicited in the area in the immediate vicinity of the appendix. This may be anywhere in the abdomen on the right or left side, under the liver, or deep in the pelvis.

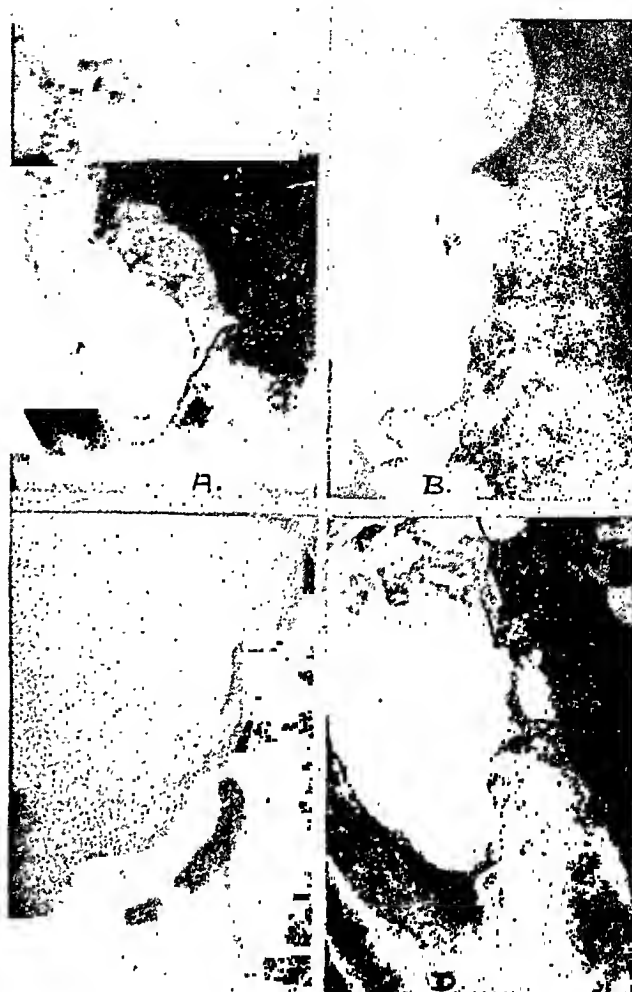


Figure 6. — Changing size of the appendix denoting normalcy. A. Appendix appearing smaller at the six hour examination. B. Same appendix appearing larger at the barium enema examination. C. Appendix appearing larger at barium enema examination. D. The same appendix appearing smaller after evacuation. If appendiceal lumen varies in size at different times in the examination, it means that the wall of the appendix is not fibrosed or edematous and that the lumen is not constricted and obliterated. This appendix can empty itself and is not diseased.

Tenderness is elicited fluoroscopically by palpating the abdomen directly over the barium filled appendix. When the appendix is the cause of this tenderness the position of the tenderness moves with the position of the appendix if the appendix is at all movable. If the appendix can not be directly visualized by barium, tenderness is elicited by palpating the barium filled cecum close to its base where the diseased appendix is apt to be and the point of tenderness moves as the position of the cecum moves. However, if the visualized appendix or the cecum are in areas remote from the area of tenderness then the appendix is not apt to be the cause of the tenderness.

Peristaltic motion and segmentation in the appendix. In evaluating segments of the appendix which are dilated and which are constricted it is important to bear in mind that normally the appendix has peristaltic movements. Deep tonic circular contractions or haustrations are seen, and these cause areas of con-



Figure 7. — Filling and emptying of the appendix. A. Filling of only the proximal end of the appendix during barium enema would suggest pathology but in the film after evacuation on "B," the distal end of the appendix fills and the proximal end empties. This denotes normalcy. B. Same appendix seen in the after-evacuation film, the distal end is filling and the proximal end is emptying. C. An appendix seen on the twenty-four hour examination. D. Same appendix still partially filled one week after the examination. This denotes a pathological appendix. Recurrent appendiceal pain was present.

striction in the appendiceal form. When the appendix is filled with barium, peristaltic waves will cause narrow areas of constriction separating homogenous segments of barium. However, this must not be confused with fecaliths, concretions or the so-called beading of the appendix. In the latter non-opaque shadows bounded by lines of barium shadows are seen.

Concretions, fecaliths, and foreign bodies. Non-opaque concretions or fecaliths appear as small, rounded, multiple vacuolated or translucent areas which resemble peas in a pod. They are non-opaque when compared to the barium about them. Fecaliths are inspissated particles of fecal matter, and are found in almost all poorly emptying appendices. Many feel they are the cause of inflammatory conditions of the appendix. Larimore (19) feels that appendiceal fecaliths are the result of a previous or coexistent inflammatory process and are not the exciting cause of the initial inflammation. At any rate fecaliths occur in about 50 per cent of cases of appendicitis and in a higher percentage of cases of perforated appendices. Fitz (11) in his cases of appendicitis found fecaliths in 49 per cent. Bowers (1) found fecaliths in 67 per cent of 372 cases of appendicitis. Bowen (2) found fecaliths in 80 per cent of abscessing or gangrenous appendices.

Royster (20) found the following foreign bodies in the appendix: bristles, pins, hair, bone, seeds, shot,

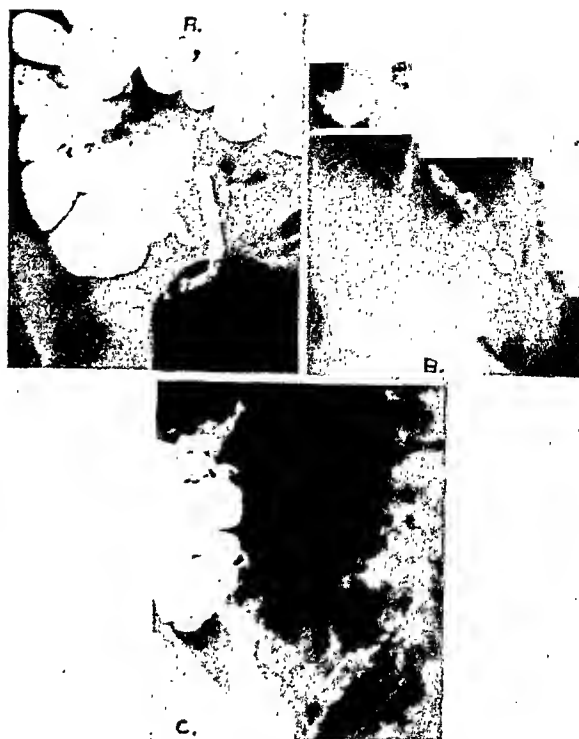


Figure 8. — Fecaliths denote a poor emptying appendix one which has had previous attacks of appendicitis and one which is very apt to have more. A. Showing fecaliths in the distal portion of the appendix with persistent kinking in its mid-portion. B. Numerous fecaliths in the distal two-thirds of the appendix. C. Fecaliths throughout the appendix.

fingernails, teeth, screws, chewing gum, apple core and nutshell. Foster and Bowers (12) found a sprouting seed in the appendix. Pin and round worms, and various ova are also found in the appendix. Fitz (11) found foreign bodies in 12 per cent of his cases of appendicitis.

Opaque concretions or stones are occasionally seen in the appendix. One-fifth of their weight is organic residue mostly vegetable fiber, one-half is fat, soluble soaps, koprosterol and cholesterol, one-fourth is inorganic material chiefly calcium phosphate which renders them opaque, Mayer and Wells (21). They arise on the basis of fecaliths and are said to occur in 1 to 2 per cent of all cases of fecaliths. Kelly and Hurdon (17) offer the following explanation for their origin. If the normal return of fecal contents from the appendix to the cecum by peristalsis is impaired in any way, inspissation of varying degrees occurs. The combination of irritation from the fecal mass and bacterial activity produces a low-grade catarrhal inflammation with its attendant secretion of mucus. Inorganic salts contained in the mucus are precipitated (probably by bacterial action) on the surface of the dried fecal particle which thus increases its size. The repetition of this process results in the lamination almost constantly present. Eventually if some complication does not intervene, the enlarging stone produces pressure atrophy in the secretory glands of the appendix and

its growth ceases. However, this pressure atrophy does not occur until very late for almost all these opaque concretions are larger than the appendiceal lumen and are firmly embedded in the appendix and can't leave the appendix as the non-opaque fecaliths often do.

The majority of non-opaque stones eventually cause acute appendicitis. In a series of 110 cases only 5 failed to present clinical and surgical findings of acute appendicitis, Felson and Bernhard (10). In this group of cases perforation occurred in 47 per cent of the 99 patients whose appendiceal wall showed gangrene. In 19 cases this resulted in an abscess and in 10 diffuse peritonitis. In 11 cases the appendix was retro-cecal and bound down to the post-cecal wall. The largest calculus they described was 2.5 centimeters in diameter and weighed 13.5 grams. The stones all showed lamination which was evident by X-ray. Multiple stones were found in 4 cases. Faceted stones were described in 8 cases.

Secondary or reflex changes due to appendiceal disease. Appendiceal disease may reflexly affect any portion of the gastro-intestinal tract. Spasm of the lower end of the esophagus and cardia can occur. It may cause pyloro-spasm and spasm of the duodenum. The epigastric pains, nausea and vomiting seen early in acute appendicitis and frequently in chronic appendicitis may be explained by these spasms. Tenderness may be elicited by pressure over the pylorus and duodenum. Pyloro-spasm may be responsible for gastric retention. White (35) found gastric delay in emptying in 7 out of 100 cases of appendicitis. Gaseous distention of the stomach may occur with a rise in the left dome of the diaphragm. Irritability and spastic deformity can occur in the lower end of the ileum and cecum. Spastic changes about the cecum and ileum are first seen in the early inflammatory conditions of the appendix. Later when the outer-most coat is involved with beginning peritonitis, then paralytic dilatation of the lower ileum and cecum occurs. Still later if the inflammation should subside, irritability and spasm of the lower ileum and cecum returns.

As a result of these changes ileal retention is quite common. At first the ileal retention is due to spasm of the ileo-cecal valve, later on it is due to paralysis or atony of the terminal ileum.

A flat abdominal X-ray examination at this stage will show paralytic gaseous distention of the cecum or of the ileum close to the appendix. In the early stages of appendicitis, spasm of the colon usually of the cecum is seen. This is also seen in chronic appendicitis. Gomez (14) found spastic colitis in 258 cases, many of them being due to appendicular reflex.

Filling and emptying of the appendix. In children, it should be possible to visualize a normal appendix with barium. At times it may be necessary to repeat the examination. Perotti and Codeca (26) visualized the appendix in 61 per cent at the first examination; in 23 per cent more in the second examination, in 13

per cent more in the third, and in the fourth the last 3 per cent. In adults barium will enter a normal appendix in 97 per cent of cases.

The pathological appendix may or may not fill depending upon whether the lumen is or is not opened. In acute appendicitis the lumen will probably be occluded as the result of edema, hyperplasia of the lymphoid tissue, inflammation etc. In chronic appendicitis it may not fill in 10 to 50 per cent depending upon the extent of the disease.

A normal appendix should fill and empty along with the filling and emptying of the cecum, even though a valve or fold exists at its opening into the cecum. A normal cecum should empty in 3 days. A hypotonic cecum should empty in 5 days. A sluggish appendix may not fill for several days and after having filled may not empty for several days. An appendix which takes longer than one week to empty is potentially pathological. It may not have to be removed at the time, it may not even be causing symptoms. One of our patients had had a gastro-intestinal series for vague lower right quadrant pain. The appendix did not empty within the first week but since his symptoms and signs disappeared he was discharged from the hospital. Six months later with recurrence of symptoms, a flat abdominal X-ray examination revealed that the appendix was still filled with the barium given 6 months before. Appendectomy revealed an acutely inflamed appendix.

The pain one feels in a sluggish appendix is probably produced when the appendix empties itself of more than the usual inspissated and dehydrated contents. It may have at the time larger fecaliths, more seeds, and cellulose than usual. The pain is of dull character, made worse by moving. Tenderness is usually not present. There is no temperature or leucocytosis. An enema or any other method of making the stools more fluid relieves the pain.

TECHNIQUE OF ROENTGEN EXAMINATION OF THE APPENDIX

A flat abdominal X-ray examination should be done first. This may show opaque appendiceal stones or foreign bodies. It may reveal gaseous distention of the stomach, the cecum and the adjacent ileum. The psoas muscle outline and lumbar spine should be studied for obliteration of the psoas muscle outline and scoliosis of the lumbar spine with its convexity to the right may indicate an appendiceal abscess. Obliteration of the shadow cast by the fatty layer in the abdominal wall close to the peritoneum may occur in appendiceal abscess, as the abscess involves the parietal wall and the fatty layer with edema and inflammatory reaction. A flat abdominal plate will visualize the urinary and biliary tracts. Most stones in the urinary tract and some in the biliary tract will be seen. When the case is not an emergency some like to do an intravenous pyelogram and study the gall bladder with priodex to rule out these two systems as the possible cause of right lower quadrant pain.

If acute appendicitis or an appendiceal abscess is suspected we like to examine the cecal region with a barium enema only. Otherwise we give barium by mouth and do a barium enema last.

The appendix is usually seen in 6, 24 or 48 hours after a barium meal. Because the appendix is not visualized at one of these periods in the examination does not necessarily mean it is diseased. It may have filled and emptied before the film was taken. At one or other of these time periods, however, it will usually be seen. It may be visualized after the barium enema and especially after evacuation of the enema. It seems that the straining of evacuating the enema causes the appendix to fill.

If the appendix does not visualize by the ordinary barium meal and a barium enema it is best to repeat the examination varying the technique somewhat. This time, however, if it is at all possible to give the patient epsom salts before the barium meal we do so. We do not give epsom salts to a patient with acute appendicitis or appendiceal abscess. As has already been said on cases of acute appendicitis and appendiceal abscesses we rarely have to do more than a flat abdominal X-ray examination and barium enema. The diagnosis of these acute conditions is readily made by the history, the physical examination, and the laboratory findings. It is usually the chronic cases we have to deal with and in these cases it is all right to give them epsom salts.

We usually give them 1 or two teaspoonfuls of epsom salts to a glass of water about two hours before we give them the barium meal. This liquefies the material in the region of the cecum and appendix, and allows them to empty their contents. It makes it possible for the barium which we give later to enter the appendix. If barium now enters the appendix we know that the lumen is not sclerosed or fibrosed, as the result of disease. After the appendix fills, it is X-rayed daily until the seventh day and every week thereafter until it empties.

The roentgen appearance of acute appendicitis. It is rarely that X-ray examination is needed for acute appendicitis. We believe that the giving of a barium meal would be a disadvantage to the patient with acute appendicitis and even a barium enema might produce more harm than good. No patient about to have an abdominal operation especially on the gastro-intestinal tract should have barium by mouth. The barium even in a normal patient becomes quite hard in the colon, sometimes hard as dry putty. In a patient operated on, with the ileus incident to the operation, and dehydration the barium becomes even harder. This hard barium doesn't go by an intestinal suture line without damage and the straining necessary to evacuate the barium does no suture any good. Even to give a full barium enema under pressure on a patient who has acute appendicitis might just be the necessary injury needed to cause a perforation. I feel the same way also about the giving of a barium meal and enema to a patient within 6 weeks after a gastro-intestinal operation.

If there is any question of doubt as to the etiology of the acute pain in the lower right quadrant probably the best and the most that should be done from the radiological point of view is a flat abdominal X-ray. This would exclude many other conditions causing right lower quadrant pain. In the majority of times a ureteral stone would be visualized in the flat abdominal X-ray examination. In urinary pathology or in the passing of a kidney stone usually a gaseous distention will occur in both the large and the small bowel, whereas in appendicitis there would be local gaseous dilatation of the cecum or terminal ileum.



Figure 9. — Acute inflammations of the appendix. A. Appendix visualized during barium enema in a case of acute appendicitis. The appendix is edematous and stands erect. This one shows gas in its distal end. B. Appendiceal abscess showing an irregularity of the cecum at its apex. C. Appendiceal abscess. Notice the pushing up of the cecum and medially of the ileum. D. Lateral view of an appendiceal abscess in a retro-cecal appendix causing a round, smooth filling defect in the posterior aspect of the cecum. See arrows.

If barium had to be given to a patient with questionable acute appendicitis who might possibly be operated on afterwards it would be better to give him a barium enema very cautiously and not under too great pressure. Then, when the cecum is filled one could determine the location of the cecum in relation to the tenderness. In acute appendicitis the chances are the appendix would not be obliterated as the result of edema etc. But tenderness would be elicited at the cecum close to the base of the appendix. When the appendix is visualized in acute appendicitis it stands straight and gives the sensation of erection, with its increase in thickness and disappearance or diminution of the curves that normally exist. Gomez (14). If the pain were due to the passing of concretions from the appendix these might be visualized by the barium enema, tenderness usually would be absent. Of course both concretions and inflammation of the appendix could be present at the same time. Tenderness would then be quite prominent. If the pain in the lower right quadrant were due to some pelvic disease such as in the fallopian tubes, or the ovaries, then either the appendix would visualize or the tenderness would be below the base of the cecum and the possible extent of the appendix.

The appendix might be present almost any place in the abdomen. Naturally it might stimulate any other abdominal disease. For instance if the patient has pain and tenderness in the upper right quadrant, the gall bladder and possibly the duodenum would naturally be suspected of being diseased. But if X-ray examination of these organs showed them to be normal and instead the cecum was found pointing upward underneath the liver and the base of the cecum and the region of the appendix showed tenderness, then the appendix would be the

cause of the symptoms. If the cecum or appendix were found in the lower right quadrant, then of course the appendix would not be the seat of trouble in this case.

Subacute and chronic appendicitis. In these cases barium can be given by mouth first and an enema is given later if necessary. If no filling occurs after a barium enema it is necessary to repeat the barium meal examination, first giving epsom salts as already described under technique.

Pathology of the appendix may be determined by 1. Tenderness over the filled appendix or over the base of the appendix if it is not visualized. 2. The inability of the appendix to fill probably because of hyperplasia or edema of the appendiceal wall and obliteration of the lumen. If the appendix fills and does not empty after one week of observation, the chances are there is enough fibrosis and degeneration of the muscular wall so that it can't force its contents out. 3. The presence of fecaliths is an indication of poor emptying quality of the appendix that water has been absorbed and the material has become harder. 4. The presence of opaque stones indicates that fecaliths have remained so long in the appendix that calcium has precipitated throughout the mass and even in layers on its surface. These opaque stones are usually larger than the lumen of the appendix and can never pass. They are adherent to the partially destroyed mucous membrane. 5. A filled appendix may show signs of disease if it shows persistent areas of kinking or adhesions. Instead of being in its usual position of slightly posterior and medial to the cecum it may extend below the cecum and may be adherent laterally. The tip may not be movable. 6. The size and shape of the appendiceal lumen give indication of pathology of the appendix. If it is very long or has areas within it, some of which are dilated and others constricted and these are persistent and are thus not peristaltic waves, the chances are the appendix is diseased. This means the lumen probably is partly obliterated, at any rate it is very hard to empty and is conducive to pathology. If the lumen is persistently short, it probably means the distal end is obliterated. 7. Retro-colic appendices don't empty well because they are bound down retro-peritoneally by adhesions and congenital bands. These appendices can't empty well and are apt to give trouble. The appendix is situated behind the cecum and ascending colon close to their lateral border. The ileum seems to come out of the apex of the cecum. 8. The presence of cardiospasm, pylorospasm with or without retention, aerogastria, irritability of the duodenum; spasm of the ileocecal valve with ileal retention; spasm of the cecum and ascending colon, indicates appendiceal disease.

The presence of the above findings are probably the result of one or numerous previous attacks of mild or chronic attacks of appendicitis or may be the results of recurrent attacks of acute appendicitis. Their significance is evaluated by the history and physical examination.

Appendiceal abscess. The incidence of abscess is about one-half per cent of surgical cases of appendicitis. The incidence of appendiceal abscesses was very much greater than it is today.

Appendiceal abscess may be situated in any portion of the abdominal cavity. It may be retro-cecal, intraperitoneal or extra-peritoneal. It may be found in the renal fossa, subhepatic, subumbilical regions, or in the pelvis. It is most commonly found in the right iliac fossa and often involves the tip of the cecum. Coils of small intestine, and in adults the omentum are usually matted together about the mass. It most often occurs in young individuals, the very old, the chronically ill or weak and stout individuals. It occurs primarily in the young because the diagnosis of acute appendicitis is hard to make in them and because the infection seems more fulminating. A long omentum is not present to localize the appendiceal infection. In the old the infection gets a start before the patient gets

many symptoms or signs. Appendicitis is more fulminating in the chronically ill especially the diabetic, in the weak and tired individuals because the tissues can't fight off the infection. In fat individuals because of poor abdominal muscle and lack of rigidity etc., the diagnosis isn't made early.

The abscess may or may not be felt abdominally. Usually in a fat individual it is not felt. At times the mass may not be suspected as being an appendiceal abscess, it may be regarded as a new growth.

The roentgen diagnosis of an appendiceal abscess is made first by taking a flat abdominal X-ray. An area of increased density may be seen in the right lower quadrant or elsewhere as the result of the inflammatory mass. If the mass is adherent to the abdominal wall or edema occurs in the abdominal wall, the fatty layer shadow may be obliterated. Gas, opaque foreign bodies or calcification may be seen within the area of increased density. The cecum and terminal ileum will usually show gaseous distention due to paralytic ileus. The abscess may be dense enough to blur the right psoas muscle outline. Spasm of the right psoas muscle may cause scoliosis of the lumbar spine with the concavity to the right.

A barium enema will usually show a smooth filling defect on the medial and posterior aspect of the cecum. The cecum as well as the lower ileum will be displaced away from the abscess. If a mass is felt abdominally it will be seen causing the defect in the cecum. The mass will be tender. There is usually ileo-cecal patency to relieve pressure on the tender mass. If the abscess becomes large enough, mechanical small intestinal obstruction may occur with much greater small intestinal gaseous distention.

Fistulae between the appendix and adjacent organs may occur occasionally. An appendiceal abscess may communicate with the ileum, the colon, the recto-sigmoid or the bladder. The roentgen demonstration of these fistulous tracts are very difficult.

Tuberculosis of the appendix is occasionally seen. It can be of the ulcerative or hyperplastic form. It occurs most frequently in patients that have pulmonary or intestinal tuberculosis. In 40 appendectomies done on patients with pulmonary tuberculosis, Steffens (30) found two cases or five per cent were tuberculous. The tuberculous appendix is not as a rule demonstrated due to the inflammatory process and in the hyperplastic type, the lumen is occluded. At times a palpable mass may be felt in the region of the appendix. The diagnosis may be suspected in a patient with pulmonary or intestinal tuberculosis with lower right quadrant symptoms and signs in whom the appendix does not fill.

Diverticula of the appendix is extremely rare. It occurs along the mesenteric border of the appendix and mostly in the distal half. It sometimes is associated with diverticulosis of the colon. It can be occasionally visualized by the roentgen examination.

Intussusception of the appendix is another extremely rare condition. The roentgen diagnosis is almost impossible. The appendix does not visualize and a tumor is occasionally felt in the lower right quadrant.

Tumors of the appendix. Benign and malignant tumors of the appendix do not give any characteristic symptoms and signs. There is usually vague pains in the right lower quadrant. A mass is occasionally felt which is less tender than an appendiceal abscess.

The roentgen signs of tumors of the appendix are few. A flat abdominal plate may show a tumor mass or density in the lower right quadrant. The mass may be felt ab-

dominantly. There may be calcification in the mass density especially in a mucocele. Barium enema may show a smooth extrinsic pressure defect on the inner medial aspect of the cecum. There may be displacement of the cecum and ileum. There is not apt to be tenderness, and paralytic gaseous distention of the cecum and ileum as in appendiceal abscess. One can't differentiate the kind of tumor although by percentage the tumor is more apt to be a carcinoid.

Benign tumors of the appendix are rare. The mucocele and the carcinoid are the most common type. Occasionally polyps, myxomas, and hemangliomas are found.

The mucocele has been described as hydrops retention of a colloid or pseudo-mucinous material. They are extremely rare, about 100 cases being recorded in the literature. The mucocele is usually due to blockage of the lumen. The obstruction may be due to a foreign body, angulation, stricture, or inflammation. The mucocele may be benign or malignant. The most common complication of a mucocele is its rupture into the peritoneal cavity producing a pseudomyxoma peritonei which is potentially malignant. A mucocele may be the cause of intestinal obstruction by pressure. The appendix usually does not visualize. When it does occasionally irregular streaks of barium may be seen within a dilated section of the appendix. Sometimes a tumor mass may be felt.

Carcinoid of the appendix. Carcinoids are so named because they resemble carcinoma of the intestine. They are analogous in growth potentialities to the basal cell carcinoma of the skin. Unlike carcinoma of the intestine they are more apt to be multiple, they have little tendency to infiltrate surrounding tissues, the growth is slow and it is not so apt to metastasize. They arise from the cells in the crypts of Lieberkuhn. The cells both of the primary tumor and its metastases contain silver reducing granules. The cells also stain with chromium salts. Thus they are often called argentaffin or chromaffin tumors.

The tumors are small in size. They are usually rubbery rather than hard. On cut section they show yellowish white, white or gray color. The cells are found in undifferentiated masses clumped in nests or strands in the submucosa of the appendix.

Carcinoids don't occur often in the intestinal tract but when they do they are most apt to occur in the appendix. According to Moore (22) 90 per cent of the neoplasms of the appendix are carcinoids. Smith (32) found 21 carcinoids in 7,865 appendices removed at operation. These tumors are usually located at the tip. They rarely extend to the proximal end. They sometimes form bulb-like masses.

Of all the carcinoids of the appendix reported only five had extended beyond the appendix itself. The extent of the metastases varied from extension to the mesentery only, to wide spread metastases in the mesentery, omentum, and in one case to the pleura. Wyatt (34). The carcinoids of the small intestines are more apt to metastasize and do so in 22.5 per cent of the cases. The appendiceal carcinoids would probably metastasize just as frequently but don't do so because they are found earlier. Their presence leads to an appendiceal reaction which necessitates their removal.

The X-ray examination of the appendix may show proximal filling if there is no acute inflammation. A mass might be felt. But the tumor is rarely suspected and rarely diagnosed.

Carcinoma of the appendix is rare. There are less than 1,000 recorded cases. Norman (25) found 57 carcinomas in 45,666 appendices removed at operation. Adeno-carcinoma is the most common histological type. It gen-

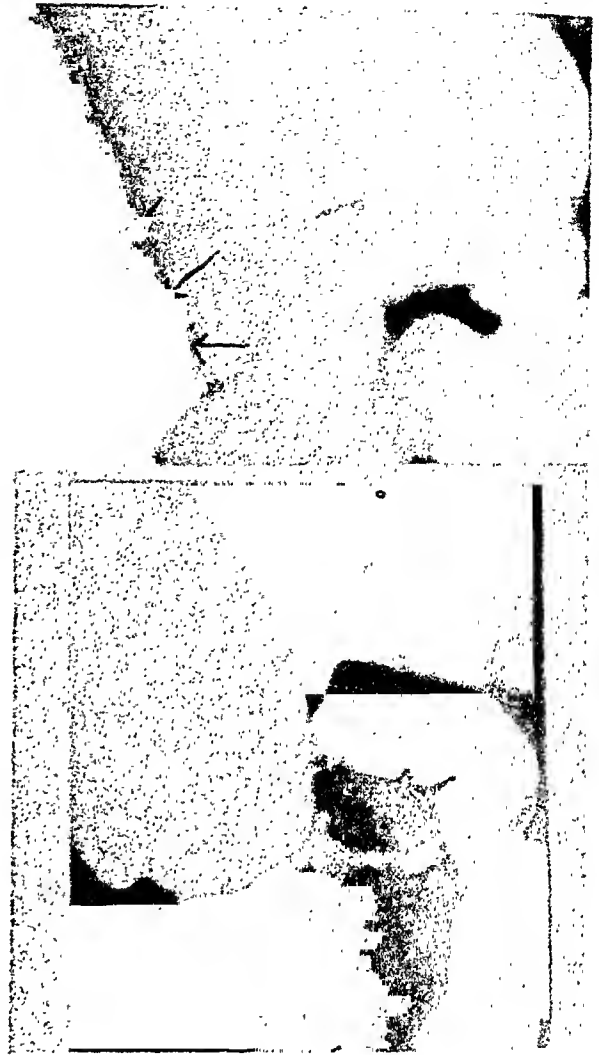


Figure 10. — A. Crescent defect (see arrows) in the lateral portion of the cecum in a case who had the appendix removed two weeks previously. B. Regeneration of the appendix seen thirty years after its removal. The stump left behind must have dilated and elongated to make possible this regeneration.

erally occludes the lumen. The tip of the appendix is the most frequent site. A mass may be palpated in the right lower quadrant which lies outside the ileo-cecal region.

Sarcoma of the appendix is extremely rare also. Seventy-two per cent of the growths were lymphoblastic and 12 per cent were fibroblastic. In 50 per cent of the cases a tumor was palpated in the lower right quadrant.

Cecal defects following appendectomy are quite common. Barium enema will show protrusion, or ring defect at the region of the appendiceal stump. Contractions in contour of the cecum may occur and evidences of ileo-cecal adhesions. Occasionally there are marked deformities with narrowing of the cecal lumen. The inverted appendiceal stump may persist as an invaginated mass protruding in the lumen of the cecum and it shows as a small rounded nodular defect at the tip of the cecum and sometimes resembles a polyp. These defects usually are seen within the first few months after the operation and should not be difficult to diagnose.

SUMMARY

1. X-ray examination of the appendix may help to lower mistakes in diagnosis. In 10-15 per cent of cases diagnosed as acute appendicitis a normal appendix is removed at operation. The percentage of appendices removed and not giving relief of symptoms in subacute and chronic appendicitis may be 25-70 per cent.

2. Roentgen examination of the appendix will give data concerning anomalies: size, form, shape, and position of the appendix; its mobility; the presence of kinks, congenital bands and adhesions; its peristaltic action; its filling and emptying; the presence of fecaliths, foreign bodies, opaque stones; and the location of tenderness directly upon the appendix; all of which data can't be obtained through a clinical examination alone.

3 Roentgen examination will disclose secondary signs of early appendiceal disease such as cardio-spasm, pylorospasm, duodenal and ileo-cecal spasm, spasms of both the lower ileum and cecum. Late appendiceal disease will show atony of the lower ileum and cecum with paralytic gaseous distention of the cecum and lower ileum.

4. The technique of roentgen examination of the appendix is given.

5. X-ray findings are discussed in acute, subacute and chronic appendicitis; in appendiceal abscess, tuberculosis of the appendix, diverticula and intussusception, and in both benign and malignant tumors.

6. Reproductions of X-ray findings of appendiceal pathology are shown.

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Endometriosis of the Ileum

By

ALBERT B. KATZ, M.D.

PHILADELPHIA, PA.

ENDOMETRIOSIS IS A FAIRLY COMMON FINDING in females who are operated upon for various pelvic conditions. Estimates of its incidence vary from eight to twenty per cent. The structures closest to the uterus are the ones most frequently involved by endometrial implants. Thus the sigmoid, rectosigmoid, and rectum are the portions of the intestine where endometriomas are most commonly encountered, and instances of the obstruction of the lower bowel by endometrial growths have been reported with some frequency. However, endometrial implants of the ileum are unusual, and they are a rare cause of small bowel obstruction. Glenn and Thornton (1) found only four cases of endometriosis of the ileum which caused obstruction and they added two cases. Wood, Deibert, and Kain (2) added a seventh case to the literature.

Endometrial tissue is subject to endocrine influence regardless of its location. Endometriomas therefore menstruate. When these tumors are enclosed, they may readily increase in size, causing pressure effects or obstructive phenomena. The following case is of interest because the timely removal of an endometrioma of the terminal ileum probably prevented frank small-bowel obstruction. It also represents some of the less typical features of endometriosis, particularly the ability of the metastatic endometrial tissue to give rise to signs and symptoms with relatively little pelvic evidence of endometriosis.

REPORT OF A CASE

Mrs. W. B., a 44 year-old housewife, was first seen on October 6, 1945. She complained of abdominal pain and fainting spells. Her symptoms first appeared in March of 1935, a year following the birth of a son. This pregnancy was her only one, and was perfectly normal. Her attacks consisted of a mid-epigastric pain and nausea which appeared shortly after the ingestion of "indigestible food." These symptoms were associated with brief spells of fainting; the latter were also precipitated by the use of strong laxatives. She had intermittent pain and a sensation of heaviness in her right lower quadrant. Her symptoms had become increasingly frequent and severe. Their appearance was not related to the ingestion of food, and they occurred about two weeks before her menstrual periods. There was no aura nor did the patient lose control of her sphincters during the brief episodes of fainting. There was no history of head injury.

The past medical history was not remarkable. Her menses began at the age of 12 years, occurred regularly every 25 days and lasted 7 days. There was rather profuse bleeding for the first three days, but there was no dysmenorrhea.

Except for deep tenderness in the right lower quadrant, and what appeared to be some induration in the right broad ligament, the physical examination was within normal limits.

Submitted November 1, 1947.

LABORATORY DATA

Repeated urinalyses were normal. The hemoglobin was 10.5 grams (Haden-Hausser); red blood cells 4,610,000; white blood cells 7,500; neutrophils 46%; lymphocytes 52%; monocytes 1%; basophils 1%. A fasting blood sugar was 82 mgs. per 100 cc. of blood; the blood urea nitrogen was 10 mgs. Stool examinations were negative for ova, parasites and occult blood. A gastric analysis was within normal limits.

Sigmoidoscopic examination revealed marked spasm at a distance of six inches above the rectal sphincter. However, the scope was passed to a distance of 10 inches and there was no evidence of disease of the lowest bowel segment.

X-ray examination showed a normal esophagus and stomach. The small bowel pattern of the duodenum and jejunum appeared normal. There was normal motility of the barium meal. A twenty-four hour film revealed some displacement of the cecum medially, the appendix was visualized and appeared to rise relatively high and laterally. There was some irregularity of the terminal ileum with flattening of the mucosal folds. (Fig. 1). No additional data was afforded by the barium enema examination.

The underlying cause of the patient's symptoms was



Figure 1. — Medial displacement of the cecum with the appendix arising high and laterally. Note the irregularity of the terminal ileum and flattening of the mucosal folds.

not clearly discernible, but the information gathered from the history, physical examination and roentgen study suggested that this patient had a lesion causing slight obstruction in the region of the lower ileum. Right adnexal disease and chronic appendicitis with adhesions were considered as possible etiologic factors.

The patient was operated upon November 6, 1945 by Dr. Norman Rothschild at the Jewish Hospital. Under spinal anaesthesia, a lower midline incision was made and examination of the peritoneal cavity revealed a normal uterus and a cyst of the right ovary. The right ovary and tube were removed. The cecum and a terminal portion of the ileum were delivered into the wound. Two inches from the ileo-cecal valve there was a constricting mass involving the wall of the ileum. It was so constricted that one could not place the third finger through the lumen. Following this examination, the appendix was removed. The portion of bowel containing the constricting mass was removed by cautery. The terminal ileum was then brought to the terminal surface of the cecum and a side to-side anastomosis was performed. The operative wound was closed and the patient had an uneventful post-operative course.

PATHOLOGICAL REPORT

Macroscopic Description: The ovary measures three cm. in diameter. It contains two rather thick-walled cysts. The tube is tortuous and kinked on itself by adhesions.

Portion of the Ileum: Mucosa appears succulent and is slightly bile stained. Second small piece of ileum: The wall appears fibrotic.

Microscopic Description: Section shows a tumor entirely surrounded by ileum (Fig. 2). The tumor presents gland-like spaces lined by columnar epithelium. The stroma consists of large ovoid cells suggestive of endometrial compacta. Mitotic figures are rather numerous in some areas. The tumor is surrounded by the longitudinal muscle coat of the ileum. One tumor fragment lies in the circular coat.

Section from the other piece of ileum appears normal.

Ovary: The wall of the cyst is lined by irregular more or less columnar cells. The tissue beneath is hemorrhagic and edematous. There are also pigment bearing cells. One place in a loculus from the main cyst is rather more suggestive of endometrium with subjacent stroma (Fig. 3).

Tube: The plicae are extremely thickened by fibrous tissue. The epithelium is heaped up and vacuolated. Small gland like spaces are found in the fibrous tissue.

Pathological Diagnosis: Ileum: Endometria; Ovary: Endometrial cyst; Tube: Nodular salpingitis.

DISCUSSION

The cause of the patient's syncope was not apparent. Epilepsy or an epileptic equivalent were considered, but there was insufficient clinical basis to substantiate either diagnosis. The syncope did appear to be related to the attacks of abdominal pain, and there was objective evidence of some obstruction of the ileum to account for the latter symptom.

Although the endometrioma was sufficiently enlarged to diminish the lumen of the ileum, it had not attained sufficient size to cause definite clinical or X-ray evidence of frank bowel obstruction. Undoubtedly the attacks of abdominal pain were caused by subacute attacks of ileal obstruction. The tumor was completely enclosed, and it is likely that repeated periodic bleeding into such an enclosed space would have caused sufficient



Figure 2. — Ileal mucosa entirely surrounds the periphery. In the center the muscular coat and several areas of endometrial epithelium and stroma are seen.

progressive enlargement to produce rather complete obstruction of the ileum.

Unlike the cases reported by Glenn and Thornton (1) and Wood, Deibert and Kain (2), this patient's symptoms appeared regularly during the mid-menstrual interval, rather than at the time of menstruation. She did not have sufficient pelvic involvement to cause dysmenorrhea, dyspareunia or menorrhagia which are common symptoms of pelvic endometriosis (3).

Because of the clinical vagaries produced by endometriosis of the bowel, its diagnosis is difficult. However, the condition should be considered in any female who presents herself during her active menstrual life with symptoms or signs of bowel obstruction, especially when she has had regularly recurring symptoms in relation to her menstrual periods. While pelvic symptoms may be minimal or even absent, as they were in the case described here, this is not the rule.

Most cases occur between the ages of twenty-five and forty-five years of age (3). If the rectum, rectosigmoid or rectovaginal septum are involved, pain on defecation, which is aggravated during the menstrual period, may be the principal complaint. When the terminal ileum is involved, obstructive phenomena may be the predominating feature. The relationship of symptoms to the menses may be the only indication of the nature of the lesion. It is therefore apparent that an adequate gynecologic history must be obtained.

Physical examination may reveal nothing of note. Frequently careful pelvic examination may reveal the presence of tenderness or masses in the adnexal areas or a retroverted adherent uterus without a history



Figure 3. — Cystic endometrial gland surrounded by endometrial stroma.

of antecedent pelvic inflammatory disease. If the rectovaginal septum is involved it may be indurated. Endometrial implants may be felt as small nodules by rectal examination.

There are no characteristic roentgen signs of this condition (4). It produces a smooth defect simulating a scirrhus type of malignancy or an inflammatory tumor. The mucosal pattern is intact, and the affected segment may be spastic. Blakley (5) noted a puckering of the bowel produced by the isolated masses, but he never encountered complete encirclement. Roentgen findings, when they are present, can be briefly mentioned as follows: 1. Mucosal pattern is not affected. 2. A circumscribed filling defect which

may be extensive. 3. Fixation of the affected bowel. 4. Absence of spasm or irritability of the segment. In addition to the foregoing may be added X-ray evidence of obstruction when it is present.

Endometriosis as it occurs anywhere in the lower gastrointestinal tract of the female initially involves the serosal surface of the bowel. There may be subsequent extension to the muscular layer. Only rarely is the mucosa involved. It is the infrequency of the latter which explains the absence of blood in the stools.

Although a careful history, physical examination and X-ray study are extremely useful in suggesting the nature of the lesion, the exact diagnosis can only be made by laparotomy and tissue examination. Since endometriomata of the bowel may be mistaken for scirrhus carcinoma and vice versa, surgical intervention not only enables one to establish the correct diagnosis, but it may be necessary as well to relieve varying degrees of obstruction. In fact, the treatment is almost always surgical. Actual removal of segments of bowel containing constricting endometriomas may be necessary, as it was in the case reported here. If there are multiple endometriomata, surgical castration is indicated to prevent further hormonal influence on the aberrant endometrial tissue.

CONCLUSIONS

1. A case of endometriosis involving the terminal ileum with early obstruction is presented.
2. The value of certain symptoms and signs are discussed which may be of value in establishing a pre-operative diagnosis of endometriosis involving the gastrointestinal tract.
3. The importance of surgical intervention as it pertains to the diagnosis and treatment of the condition is discussed.

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Protein Supplementation in Gastro-Intestinal Diets

By

ALFARETTA JOHNSON, M.S.

LOS ANGELES, CALIF.

IN THE FOLLOWING REPORT of a case of ulcer, emphasis is placed on the possibility of supplying the patient a diet high in an assortment of needed amino acids. When meat, fish, game and fowl are contraindicated in the medical management other protein foods must supply the amino acids that would have been furnished by these foods. One possible method of providing the array of essential amino acids is by supplementation of proteins. This concept of protein supplementation is not new. Reports in the literature have suggested that the biological value of proteins is in relation to the essential amino acids which they contain (1) (2). Foods offered to the ulcer patient are protein foods of high biological efficiency but of a bland, non-stimulating, non-irritating type.

In the evaluation of a group of foods for their nutritional value, the appraisal must be based not only on the content of a single food factor, but rather on the multiple nutrients present in the particular food. Amino acids are used for patterned reparative responses along with other nutrients for the patient. Menu planning is concerned with the nutritive value of diets, which is a mixture of several foods, each of which makes a distinct contribution.

In no therapeutic diet regime are results so dependent upon understanding of the diet as in the dietary management of gastro-intestinal patients. The success or failure of both the patient and the dietitian, or, doctor are bound up with the energy, materials and time available for constant instruction. The requirements of protein in the diet are high because during convalescence Roche (3) reports an abnormally large turnover of dietary proteins to be essential. In partial degeneration of muscle proteins, as in wasting diseases, the mono-amino acids are increased, the di-amino acids greatly decreased, and cystine, histidine and arginine remain constant. Tryptophane and lysine are diminished in amount. Essential amino acids which can be replaced by the corresponding alpha-keto or alpha-hydroxy-acid according to Neuberger (4) are leucine, isoleucine, valine, methionine, phenylalanine, tryptophane and histidine. Essential amino acids which are not replaceable by the corresponding alpha-keto or alpha-hydroxy-acid are lysine and perhaps threonine. A deficiency of essential amino acids cannot be made up by an abundance of the so called non-essential amino acids. Here a deficiency is defined as any condition which will be benefited by an increase in amount of a specific amino acid, or, a change in the

proportions to other materials supplied that influence the need for that specific amino acid.

There have been reported variations in the proteins of the various organs in their ability to fix dietary nitrogen. The proteins of the internal organs, of serum and of the intestinal tract are most active as acceptors of dietary nitrogen according to isotopic analyses; the proteins of the muscles, less active and those of the skin, least active. The transfer and replacements of individual amino acids within a single protein molecule must necessarily involve the constant breaking open of existing peptide bonds and the creation of new linkages. Plasma proteins are not static but reflect tissue stores. There is a constant state of flux.

Like the carpenter who can replace the old worn out door with a new one without completely tearing down the building, the body merely removes the old, worn-out amino acid from the protein undergoing repair and inserts the new one without destroying the original structure of the protein. Chemical synthesis of amino acids yield equal amounts of the levo and dextro forms, (5) but in nature the levo occurs predominantly, and in many cases, is the only form utilizable in man.

The functions as indicated by Goth and Biskich (6) of proteins and amino acids cover a wide range, including bacteriostatic action, detoxifying action and specific ketoplastic action.

In supplemental relationships the strength of the mixture results from the union of two or more foods. Both foods must be fed at the same time, and sufficient amounts must be offered if this supplementary relationship is to exist. Meals providing from two to three protein-containing foods supply the assortment of building stones that can be fitted together to make the needed pattern. The deficiencies of one protein food will be made up by the excesses of the limiting amino acids in other protein food, provided the diet is mixed, varied and alternating.

Cereal foods furnish an example of the way that protein supplementation occurs. The protein of wheat is not a complete protein. It is deficient in at least one of the essential building blocks (lysine) and without this amino acid it cannot do a complete job of body building. Milk is rich in lysine but has methionine and cystine as the limiting amino acids. In each case the limiting amino acid is not the same. Thus when milk is used with bread or cereal, the combination of

Clinic Dietitian, College of Medical Evangelists, Los Angeles.

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the two makes the protein of the grain more fully useful.

Estimations of the biological value of proteins may be made from the standpoint of their content of each essential amino acid. Estimations of the efficiency of the protein foods offered to the ulcer patient are more than a quantitative estimation of the number of grams of protein. An evaluation must be made of the supplementary relationships. The terms "first class protein" and "second class protein" are meaningless when applied to mixtures of dietary protein because of the supplementary relations which exist.

It is known that the supplementation value of vegetable proteins is great. Small amounts of proteins such as milk and eggs combined with plant proteins of lesser concentration result in a combination which will support growth and reproduction in animals. This is true if the same limiting amino acids do not exist in both sources, or that the milligram need is met. For example it is estimated that 600-1000 mg. methionine is to be insured daily. If the daily mixed diet does not furnish that specific need it cannot be accounted a source of adequate protein regardless of the number of grams of other amino acids the order includes.

Daily amino acid requirements for children and adolescents up to 77 lbs. are estimated to be: Arginine 1.0-1.7 grams (per day), Histidine 1.0, Lysine 3.0, Tryptophane .8, Phenylalanine 2.2, Methionine and Cystine 1.0, Threonine 1.7, Leucine 4.6, Isoleucine 2.8 and Valine 3.0.

Studies show that diets high in protein of poor quality may be more harmful than diets low in protein but having the essential amino acids in good proportion.

Several foods which are coming into play in recent years are flours from seedmeals. Seedmeal flours may be whole fat or partially defatted or low fat. Flours prepared from soybeans, sunflower seed meal, partially defatted peanut flour and cotton seed meal (Proflo) contain proteins of high nutritive value and may be used to partially replace proteins of animal origin. Fine grind defatted wheat germ and corn germ are available at VioBin Corp., Monticello, Illinois. These cereal germs can be incorporated into the low residue diet. These flours and fine milled germs can occupy 1/6th of the total volume of various cereal foods, batters and doughs, breads and pastes. Soybean flour proteins are valuable in making up the amino acid deficiencies of wheat and corn. Lysine is inadequate in wheat proteins but abundant in soybean. Peanut proteins, as occurring in the fine milled defatted (partially) flour may be a valuable supplement for the amino acid deficiencies of corn proteins and of wheat proteins. In all cases the fine grind wheat is superior to the unenriched white patent flour as a food to which supplementary seed meal flours may be added.

Protein foods for the ulcer patient and those with modifications of the diet due to gastro-intestinal conditions include:

Milk, fluid, dried, evaporated, reconstituted and flaked. Dried whey powder, lactalbumin. Edible casein, such as Casee. An assortment of various immature, bland vegetables to be cooked with seed meal flours. Have non-fat milk solids incorporated in protein rich main dishes allowed.

Samples: cooked mashed yellow squash with soybean flour, cream of potato soup with defatted peanut flour, green pea soufflé with cotton seed flour (Proflo), Fondue with defatted flbert or Brazil nut flour.

Enriched or fine grind whole grain cereals with bran and husk removed and with added extra fine defatted wheat germ and corn germ or gluten flour with added fine milled cereal germs and seed meal flours.

Defatted seedmeal flours as soybean flour, cottonseed flour, sunflower seedflour, sesame seed flour, partially defatted peanut flour, chick pea flour, lima bean flour.

Defatted nut flours — flbert flour, brazil nut flour, partially defatted almond flour. Dried brewer's yeast. Soya cheese or curd or Tofu. Cheese of the soft and low fat varieties as low fat skim milk Jack cheese. Eggs, whole or dried or frozen. Fortified breads in which 3-6% of the flour is replaced by soybean flour, non-fat milk solids, whey powder or edible casein. Soybean sprouts and Mung bean sprouts.

While large amounts of some of these foods may not be used, several kinds used in one day will aid in supplementation of proteins with larger amounts of bland foods predominant in the diet.

Supplementation with only the few critical amino acids in which the dietary supply is inadequate will increase protein utilization as effectively as supplementation with all ten or more so called Grade A essential amino acids.

Malnutrition has been reported to develop when there were an abundance of non-essential amino acids present. Foods are measured in their growth promoting, plasma building, and tissue regenerating value. The proportion of the protein in a high protein diet — such as is offered to the patient needing to build gastro-intestinal tissue — ranges from 15-20% of the total calories. If any one of the amino acids required for the synthesis of a given body protein be lacking, that structure cannot be formed regardless of how great a surplus there may be of the other construction parts. Quantity of protein and quality of protein are important.

Protein is supplied most readily if there are sufficient calorie-carrying foods to provide a wide assortment of protein contributing foods. On low calorie diets, it is difficult to get restricted intakes to furnish amino acids from as many sources since some of the highly concentrated protein sources are concomitant carriers of factors not indicated on the bland diet. Protein foods which have been suggested for their supplementary value are: defatted peanut flour, 0% protein; dried whey powder, 12% protein; dried brewer's yeast, 45-51% protein; fine grind, defatted wheat germ 35% protein; fine grind, defatted corn

* flaked milk is milk, skimmed and the butter fat is replaced with other animal or plant fats.

germ 20% protein; gluten flour, 41% protein*; non-fat-milk solids 35-41% protein; partially defatted almond flour, 39.5%; lima bean flour 21.5%; soybean flour, 1% fat or less, 44.7% protein; soybean flour 7% fat, 42.5% protein.

A few protein food combinations with other foods which mixed lead to increased protein efficiency through supplementation are:

Enriched bread or cereal grains with seed meal flours such as cooking converted rice with 3% by weight of soybean flour. Oatmeal, fine milled with non-fat-milk solids. Potato with non-fat-milk solids or soybean milk or defatted nut flour of brazil nuts (Note: brazil nuts are a very rich source of sulfur containing amino acids). Tubers and green leaves with egg proteins. Green leaves and sprouts with milk and non-fat milk solids and soybean milk. Dried brewer's yeast used at a meal containing grains and vegetables, pigmented Laetalbumin added to fruits allowed or fruit juices allowed. Defatted corn germ or defatted fine milled wheat germ with other grains. Soya cheese or curd with potatoes and root vegetables and allowed legume flours.

When making out menus the meals are discussed in terms of taste, color, texture, consistency, and balance-of-constituents in the prescribed diet. Mashed potatoes, for example are soft and moist, but baked potatoes, in their crisp brown jacket, are dry and mealy. The object of the menu planning is to have the consumption of foods in the most acceptable form.

Case: The patient placed on the modified residue, supplementary protein diet who was worked up by Drs. Coggin, Comstock and Lilly was reported to need this diet because of the following findings:

A 8783-Roentgenologic report No. 1. — Patient male, age 57, on ulcer treatment three weeks. The chest, on fluoroscopic examination, was normal in all respects, except for a moderate amount of left ventricular enlargement, and slight redundancy of the aortic arch. The esophagus was normal throughout. The stomach was high in the abdomen and hypertonic. The rugal markings were definitely coarse and irregular. Peristalsis was vigorous, and no constant filling defects were seen in the stomach shadow. The duodenal cap was small and irregular. Distal to it was an enlarged portion of duodenum. Each of the films taken show the stellate configuration characteristic of duodenal ulcer, and at the upper portion of the shadow, there is suggestion of a constant niche. There was considerable amount of tenderness over the duodenum. At six hours the stomach is empty, although there is a small amount of barium clinging to the rugal folds in the stomach area. The meal has advanced to the terminal ileum and cecum. Conclusion: Duodenal ulcer.

A 8783-Roentgenologic report No. 2. — one week later:

Because of findings on previous X-ray examinations incriminating the pyloric end of the stomach, the patient was subjected to further study under the fluoroscope to determine the exact nature of the changes noted. Films taken in the series just completed in this laboratory gave evidence of duodenal irritation, and presented irregular stellate shadows in the region just above the pyloric end of the stomach, which were superimposed upon the shadow cast by barium in the intestinal loop behind the stomach. The patient was given one swallow of barium, and by manual pressure a niche was demonstrated in the lesser

curvature near the pylorus. The niche was irregular. Its base did not extend below the normal border of the stomach, and it was surrounded by a clear area when pressure was applied, giving the typical meniscus sign. Fluoroscopic findings did not give as conclusive evidence of duodenal ulcer as we thought in the previous examination. The presence of a duodenal ulcer was however not ruled out, and a definite cap irritability was demonstrated. The niche with the meniscus sign was nicely demonstrated on a spot film. Conclusions: The presence of an ulcer on the lesser curvature of the pyloric end of the stomach is conclusively demonstrated. Its appearance, along with the demonstration of the meniscus sign, makes it probable that the ulcer is neoplastic in nature. The presence of duodenal ulcer or reflex irritability, must be considered.

MODIFICATIONS FROM THE NORMAL DIET OR THE NUTRITION OF THE PATIENT UNDER SPECIFIC DIETARY ORDERS MODIFYING COMPLEMENT OF ANY DIETARY FACTOR

Bland Diet Indications:

Ulcer, hyperchlorhydria, gastritis, cancer of the stomach in which dietary management might be a therapeutic measure, increased gastric motility, colitis.

Principles of the diet:

To provide a diet as adequate in nutrition as possible without being mechanically, chemically, thermally or bacteriologically stimulating. Toxic materials are avoided. Small feedings are given ulcer patients. Offer low residue soft foods which have the cellular content subdivided or altered by cooking, and also reduce the peptic substances in the food. Avoid foods causing stimulation of gastric activity. Offer protein foods which act as buffers at each feeding. Frequent feedings of foods dilute the stomach contents.

Bland diet consists for example of:

- 1 quart of milk and not over 6 cups.
- 1 protein rich main dish equivalent to 3 ounces lean cooked meat, fish or fowl or large portion cottage cheese, soycheese, Tofu.
- 2 eggs or 1 egg and a substitute as cottage cheese, cream cheese or soybean flour.
- Table fat — 1 ounce plus or minus depending on the total calories.
- Bread or cereal, milled or very fine grind — 2 ounces.
- Fruit — 2 portions of 4 ounces each cooked.
- Fruit juices, citrus from 4-6 ounces used as a part of the meal and not to be offered on an empty stomach.
- Vegetable — colored, strained; possibly other vegetables in soup.
- Potato — 1.

Low Fiber diets:

Allow foods containing a minimum of indigestible cellulose, as come from fruits, vegetables and whole grain cereals. No tough connective tissues. Foods cooked to reduce the volume and make the cellulose soften. Mechanically prepared much like bland diet.

Low Residue food choices:

Bread: White bread enriched not fresh; avoid bran or coarse whole grains as occur in pumpernickle or whole rye bread with seeds, caraway.
Use plain white or enriched toast or melba.
Offer low fat crackers, zwieback or rusks.

Fat: Vegetable or plant fats hold up better if used in cooking. Limit all table fats to small amounts of enriched margarine or butter.

Cereal foods: Rice, enriched or restored, refined prepared or ready to cook. Small quantities of allmentary

* Gluten flour is lacking in lysine, one of the essential amino acids, but if used in conjunction with dairy products the deficiency can be made up.

pastes such as spaghetti, noodles, macaroni.

Desserts: Small amount of not too sweet plain puddings, such as tapioca, rice cornstarch, custard, whips, junket, Bavarian cream, Jello, occasionally ice cream, sponge cake, angel food cake, arrow root cookies, but avoid mincemeat pies, spice cake, gingerbread and very rich desserts, doughnuts.

Eggs: Any way but fried.

Cheese: Cottage, cream or mild yellow cheeses used in cooking.

Fruits: Cooked, free from seeds, stones, skins as apples, apricots, pears, peaches, plums, prunes, Royal Anne Cherries, banana, ripe avocado, or juices and puree of berries, apricot, tangerine, pomegranate, grapefruit, grape, prune, pineapple, orange, lemon, grapefruit or other citrus combinations.

Avoid: Berries, raw apples, melons, or those with tough outer skins as grapes.

Meats, Fish, Fowl: Roasted, baked, boiled, either lean or deprived of all fat before cooking. Scrape tough cuts before cooking. Avoid pork. Do not use smoked, salted or spiced and pressed meats. When supplementation of protein is practiced the amount of meat, fish and poultry can be reduced or eliminated. If meat is allowed it is on the doctor's order.

Soup: Cream soups made from cereal products and vegetables allowed. Avoid meat stocks, broths or bouillons with meat extractives. Salt in moderation but avoid all other spices, seasonings and condiments. Sugar in moderation. Avoid concentrated sweets as candy, liberal use of jelly.

Vegetables: Include cooked white potato, strained sweet potato. Use no tough skinned or stringy vegetables or those in the cabbage and onion family. Include asparagus tips, beets, immature carrots, peas hulls, string bean puree, strained greens, baked or cooked squash, tomato juice and various vegetable juices.

Beverages: Avoid soft drinks, alcohol, wine, coffee, tea, cocoa or chocolate. Occasionally may use non-stimulating beverages made of milk and fruit juices. Milk, cream and dairy products made of milk.

Note: Adjuncts to the diet may include the fine grind corn germ and wheat germ defatted which can be obtained from Vio Klin Corp, Monticello, Ill. Brewer's yeast on the doctor's order.

See: J. A. M. A. 128, 5, June 2, 1945, Clark, W. E. "Gastrointestinal Conditions."

GENERAL MEAL OUTLINE INDICATED FOR LOW RESIDUE DIET ORDERS AS IN SPASTIC CONSTIPATION, DIARRHOEA, COLITIS, DIVERTICULOSIS, DIVERTICULITIS, HEMORRHOIDS, PARTIAL INTESTINAL OBSTRUCTION, ENTERITIS, DYSENTERY FOLLOWING CERTAIN INTESTINAL OPERATIONS:

Breakfast:

Cooked or prepared milled cereals.

Egg — cooked in some form other than fried or scrambled in grease.

Enriched white toast.

Table fats in small amounts.

Strained cooked fruits or citrus juices.

Milk.

Noon Meal:

Main dish rich in protein such as omelet, fondue, souffle, cheese dishes.

Potato.

Strained or immature vegetables.

Enriched white bread plain or toasted.

Table fat in small amounts.

Milk.

Desserts a few times a week.

Night Meal:

1/2 cup tomato juice or citrus juice if not used in meals above.

Cream soup made of vegetables allowed.

Egg or cheese or portion of protein rich food is allowed.

Potato or substitute, or two portions other vegetables.

Enriched white bread.

Fruit.

Milk.

Recipes:

General Directions for making omelet:

2 Eggs — separated.

4 tablespoons milk.

Pinch of salt.

Separate the eggs and add the milk to the yolk. Beat. Add the salt to the whites and beat until stiff but not dry. Fold the two mixtures together and pour into hot omelet pan, brown on one side of top of the stove and then put in oven to brown the top. Serve hot.

General Directions for making vegetable cream soup:

1 cup milk.

2 tablespoons fat.

2 tablespoons flour.

1/2 cup puree of vegetables.

Heat the milk, blend the fat and flour together and combine with the milk, heat 3-5 minutes over double boiler and then add vegetable puree. Salt to taste. Serve hot.

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Editorial

RACIAL WISDOM IN FOOD SELECTION

IT IS PROBABLY TRUE that a race under comparatively primitive conditions will, in time, select as a group, those foods in their environment which provide the best nutritive advantages. Crude trial and error methods no doubt result, after many generations, through the law of survival of the fittest in food traditions and eating habits which best suit the individuals living under constant conditions of climate and work. This idea of *safety* in an evolutionary system of food selection has long been considered probable and it gains a very great deal of support as a result of the excellent and fundamental work in food analysis being carried on, over a period of years, at the Massachusetts Institute of Technology, because this work has already demonstrated, in scientific fashion, that some of the primitive peoples of Mexico and of Middle America, whose foods differ from the American diet most radically, obtain from their herbs and plants much better supplies of nitrogen, calcium, iron, carotene, thiamine, riboflavin, niacin and ascorbic acid than we obtain from our customary urban diets. The Otomi Indians in the Mezquital Valley of Mexico, although partaking of very few of the foods which are considered essential to a good nutrition pattern, seldom showed pronounced clinical nutritional

deficiency. The consumption of meat, dairy products, fruits and vegetables was extremely low. As Dr. Robert S. Harris points out, "there are many parts of the world where the American pattern of good nutrition should not be advocated because the food stuffs which assure good nutrition for us are not often those which can most effectively and economically nourish the people of other countries."

Not only should this lesson be learned by us but we ought to understand also that in a complex industrial nation such as ours, many of the foods which we select have been modified, sometimes drastically, by the methods of processing them, so that we may lose some of the virtues of an early American diet which reflected the racial wisdom of our own continent. Probably we do not as yet know the full story of the nutritional value of foods and there may still be important, undetected vitamins and food principles, to say nothing of the unexplored physiology of the trace elements. A "back to nature" movement will receive impetus whenever we discover that civilization brings error as a counterpart of its growing complexity. Our pride in a new science of nutrition ought not to displace reverence for the very fundamental value of racial wisdom in food selection.

ERRATA

In the January 1948 issue on page 6, under Discussion in the first sentence of the second paragraph, the word "leucopenia" should read leucocytosis," and in the last paragraph, "leucopenia with" should read "leucopenia in."

Book Reviews

TREATMENT BY DIET. By Clifford J. Barborka, M.D., 5th edition. 784 pg. 13 color plates, one black and white plate. (\$10.00) J. B. Lippincott, Philadelphia. 1948.

Barborka has used the fifth edition of his book "Treatment by Diet" to rewrite many chapters and to improve the book on a wide scale. Since the last edition in 1939, the knowledge of vitamins in diet has advanced and Barborka takes, of course, this opportunity to give detailed, new suggestions. The daily allowance and therapeutic dosage of vitamins is discussed. Tables to recognize vitamin deficiencies are given and a new chapter with many illustrations has been included.

The section on liver diseases has been rewritten to incorporate the newer conceptions of the application of protein. Besides, it describes the use of choline and other food factors utilized in treating cirrhosis of the liver, chronic hepatic diseases, and hepato-cellular jaundice. In the chapter on diabetes mellitus, all diets with less than 100 grams of carbohydrates have been eliminated. Tables are added for up to 250 grams of carbohydrate intake.

Very important chapters have been added on diet treatment of skin diseases and on preoperative and post-operative care.

Among the chapters which we consider of im-

portance may be mentioned: the diet in febrile diseases, in intestinal diseases, food allergy, and pregnancy.

The tables are given in two ways, the one, the quantitative total food allowance for one day, and, on the opposite page, a table of the suggested distribution of the food per day. The amount of food is given in grams and in household measure, which simplifies the application of carrying out the diet.

The book contains innumerable charts and 13 colored plates. The type is clear. An extensive bibliography (37 pages) and a good index, make the book very useful. Diet, being such an essential factor in our therapy, we can only congratulate Barborika on bringing his book up-to-date so efficiently. It will find many readers, not only among gastro-enterologists, but practically among all branches of medicine.

FRANZ J. LUST.

MODERN TREATMENT OF PEPTIC ULCER. By Asher Winkelstein, M.D., Pp. 205. (\$4.00), Oxford University Press, New York, 1948.

In recent years several monographs on peptic ulcer have appeared. Winkelstein's present book covers the title subject in an interesting, instructive and exhaustive manner. The 22 chapters cover etiology in relation to therapy, the pathological physiology of gastric secretion in ulcer, modern surgery including vagotomy, subtotal gastrectomy and gastroenterostomy and de-

votes considerable space to the author's intragastric drip method which has found great clinical utility. An extensive bibliography is included which will prove helpful to all readers, investigators, gastroenterologists and indeed all students of this controversial disease. The book ought to be studied by every physician and surgeon who desires to clarify his own ideas on the treatment of ulcer since it would be difficult to imagine a more satisfactory treatise.

HYMAN I. GOLDSTEIN, M.D.

PROTEINS AND AMINO ACIDS IN NUTRITION. By Melville Sahyun, M.A., Ph.D., Pp. 566. (\$8.50), Reinhold Publishing Corp., New York, 1948.

Dr. Sahyun has edited a most valuable book on the role of proteins and amino acids in nutrition and has himself contributed the chapter on plasma proteins in their relation to nutrition. The other contributors are prominent clinicians, physiologists and biochemists. Apparently all conceivable and important aspects of the problem are presented in a rather exhaustive manner. The chapters dealing with the economic aspects of meat and meat products are as stimulating as the clinical sections dealing with proteins in pediatrics, pregnancy and surgery. Perhaps the chapter on the protein nature of filterable viruses is the most fascinating of all. The book is illustrated and contains a long and very acceptable table showing the proximate composition of American food materials.

Abstracts Of Current Literature

ABSTRACT EDITOR — M. H. F. FRIEDMAN

Jefferson Medical College

1025 Walnut Street

Philadelphia, Pennsylvania

CLINICAL MEDICINE

MOUTH AND ESOPHAGUS

NEUHAUSER, EDWARD B. D. AND BERENBERG, WILLIAM: *Cardio-esophageal relaxation as a cause of vomiting in infants.* (Radiology 48,5480, May 1947).

Persistent relaxation of the hiatus esophagus is an important but rather infrequent cause of vomiting in the newborn or young infant. Twelve patients with this condition have been seen during the past three years. The clinical picture of persistent regurgitation that can be alleviated when the patient is placed in the erect position suggests the diagnosis.

The diagnosis can be made with certainty only by fluoroscopic examination. Retrograde filling of the

esophagus during inspiration or with increase in intra-abdominal pressure with persistent relaxation of the hiatus esophagus is diagnostic. The condition appears to be, in the majority of instances, a temporary aberration of the neuromuscular function of the hiatus portion of the esophagus and diaphragm.

FRANZ J. LUST

BOWEL

BLACK, B. M., AND THOMAS, J. F.: *Skin-grafted ileac stoma.* (Proc. Staff Meet. Mayo Clinic, Oct. 29, 1947, V. 22, No. 22, 503-512).

The only surgical procedure which has consistently proved beneficial in the major complications of ulcerative colitis is the creation of an ileac stoma to divert the fecal stream. (The colon later usually

is removed). The complications which indicate this operation are—diffuse polypoid disease, marked strictures, extensive peri-rectal abscesses, malignant lesions, subacute perforations, massive hemorrhages and intractable colitis. The Dragstedt technique has been followed in four cases, using skin grafting of the stoma, which has reduced the perils of skin inflammation to zero.

ZANCA, MAJ. PETER: *Gastrocolic fistula complicating carcinoma of the colon.* (Radiology 48, 3, 244. March 1947).

The roentgenological findings in this case were the following. Oral administration of the barium showed a normal esophagus. The contrast substance passed from the stomach immediately into the descending colon. Only a small portion of the barium meal passed into the duodenum, outlining a normal duodenal bulb. There was an irregular filling defect of the pars media, involving the greater curvature of the stomach. The barium passed from this region through a long, irregular tract into the splenic flexure of the colon. The greater part of the gastric mucosa appeared coarse and irregular. At the six hour examination the stomach was empty and the head of the barium was in the cecum. The gastro-colic tract remained filled; the distal third of the transverse colon and the upper portion of the descending colon were also filled with barium. The connection between the splenic flexure of the colon and the stomach was very well visualized after a barium enema. The operation revealed the large tumor mass originating from the distal portion of the transverse colon involving the greater portion of the posterior wall of the stomach and containing the gastro-colic fistula.

FRANZ J. LUST

McGIVNEY, J.: *Perianal and perirectal infections.* (Texas State J. Med., V. 42, p. 587, 1947).

The anatomy of the anorectal region is described in detail to show the devious pathways provided for the spread of anorectal infections. The beginning of nearly all perianal and perirectal infections is in the vicinity of the anorectal margin which includes structures such as intramuseular glands, ducts, crypts, rectal columns and anal papillae. Drainage of the areolar tissue of the pecten is into the anal canal and the anal crypts. The areolar tissue is poorly vascular and the constant trauma to the anorectal region which always contains pathogens makes possible infections and suppuration. Anal fibrosis may result from chronic infection. The anal intermuscular septum at the point of junction of the areolar tissue is frequently the site of fistular openings.

Cryptitis and papillitis constitute the first phase of infection and the condition may be entirely silent. Extension of the infection into the second phase consists of spread beneath the skin of the anal canal through the internal and external sphincters into the perivirectal space. Abscess formation in the peri-

anal and perirectal areolar tissues characterizes the third phase. Rupture of the abscess with formation of a draining fistula constitutes the fourth phase.

The only treatment is surgical removal of the fistulous tract with such adjacent tissue which may be diseased.

D. A. WOCKER

THOMAS, SYDNEY F.: *Appendiceal coproliths: Their surgical importance.* (Radiology 49, 1, 39. July 1947).

The importance of the diagnosis of appendiceal coproliths is emphasized, especially since it is believed that such a diagnosis warrants operative intervention. The author reports six cases of appendiceal coproliths, in four of which the seriousness of the disease following rupture of the appendix is emphasized. One of the four largest coproliths yet reported — 3.0 by 1.5 cm. — is included in this report.

When the diagnosis of "chronic appendicitis" is entertained, a roentgenogram of the abdomen with the patient supine should be made to rule out the possibility of a calcified appendiceal coprolith. But one must remember that the diagnosis of chronic appendicitis is impossible roentgenologically. It is only inferred that, when a clear-cut history fits with the roentgenographic diagnosis of an appendiceal coprolith, operation for chronic recurring appendicitis will yield benefit.

FRANZ J. LUST

SAMPSON, D. ALAN AND STAUFFER, HERBERT M.: *Rupture of small intestine complicating injury of pelvis.* (Radiology 49, 1, 80. July 1947).

The authors describe two cases of damage to the small intestines with recovery after delayed diagnosis and recovery. In the first case the condition was found two months after the accident. The patient was suffering of bouts of vomiting. There were abdominal pains. The roentgenological examination of the gastro-intestinal tract revealed a normal stomach. The small intestines showed an obstruction in the lower abdomen near the midline. Spot films taken seventy minutes after oral administration of barium showed a region of narrowing of the small intestines, the jejunum proximal to this obstruction was grossly dilated. Although the head of the barium column entered the cecum at five hours, there remained localized collections of barium in the small intestine in the lower abdomen, even at the 24 hour examination. The laparotomy revealed a complete transverse laceration of the terminal ileum, which had been walled off by inflammatory tissue consisting of omentum and part of the sigmoid, which had been drawn over.

The second case was examined one year after the accident on account of recurrent pains and tenderness in the right lower quadrant of the abdomen. The roentgenological examination after oral administration of barium revealed an attenuated segment of term-

inal ileum several centimeters in length immediately proximal to the ileo-cecal junction. Marked distortion of the cecum was noted. The operation showed that the transverse colon and a loop of ileum twelve inches from the ileo-cecal valve were found bound in a mass involving these two structures, and the cecum. This mass was adherent to the posterior portion of the ileac bone at the site of an area of inflammation in the region of the ileo-cecal valve.

It is remarkable that both cases survived in spite of delay in diagnosis and operation.

FRANZ J. LUST

GERWIG, W. H. JR.: *Diverticula and other mucosal-lined and pathological outpouchings of the gastro-intestinal tract.* (Am. J. Surg., V. 74, p. 462, Oct. 1947).

The author discusses diverticulae of the alimentary tract according to their locations in an aboral direction. He cites illustrative cases for each which serve as examples of the clinical signs and symptoms and surgical findings which might be found. X-ray plates are used to bring out the roentgen features. Gastric diverticulae are quite uncommon, and of the 150 cases reported by Moses, only about one-third gave rise to symptoms. Congenital and acquired transdiaphragmatic herniations are discussed and operative cases described.

MEILING, R. L.: *Appendicitis complicating pregnancy, labor and puerperium.* (Surg., Gyn. and Obs., V. 85, p. 512, Oct. 1947).

The author presents a thirteen year statistical summary, showing the incidence of abdominal disease complicating pregnancy gathered from the records of the University Hospitals of Cleveland. He also calls attention to the masking or alteration of the usual accepted clinical signs and symptoms, as well as the established laboratory findings used in making a diagnosis of acute appendicitis in the presence of pregnancy. Four case histories are presented of patients with acute appendicitis complicating labor or the puerperium which occurred in Cleveland during 1945 to 1946.

During the first 7 1/2 months of pregnancy the author considers that the best treatment of appendicitis is prompt appendectomy with a minimum manipulation of the uterus followed by gastro-intestinal decompression, blood transfusions and the intravenous administration of plasma and fluids supplemented by sufficient administration of chem- and antibiotic therapy. Some recommend post-operative administration of estrogen-progesterone to reduce the possibility of abortion or premature labor. Then the problem of appendicitis occurring during the last 2 1/2 months of pregnancy is considered especially when the appendix has perforated and peritonitis develops. In such cases the author recommends Caesarian section (low transverse laparo-trachelotomy) followed by appendectomy and the intra-peritoneal implantation of five to ten grams of sulfanilamide or sulfathiazole crystals followed by massive doses of penicillin for several days. These

procedures should be accompanied by gastro-intestinal decompression and the administration of blood and plasma. The patient receives nutrition intravenously.

DOUB, H. P.: *Malignant tumors of small intestine.* (Radiol., V. 49, p. 441, Oct. 1947).

Malignant neoplasms of the small bowel occur more frequently than hitherto believed. The commonest neoplasm is the adenocarcinoma, followed in order by lymphosarcoma and the carcinoid tumor. Constricting tumors tend to obstruct the bowel by decreasing the lumen size while polypoid tumors produce obstruction by either intussusception or their very physical mass. Weight loss and decreasing strength, anemia, and pain are characteristic. Obstruction, distention of the abdomen and hyperperistaltic activity may be found. Jaundice may indicate obstruction or involvement of the ampulla. The symptoms and clinical signs of tumors in the duodenum, jejunum and ileum are similar. The rate of growth of the tumor will influence the sequence of symptoms but loss in weight and strength together with anemia and a palpable abdominal mass are very suggestive, particularly if there has been a change in bowel habits.

PANCREAS

SPRAGUE, R. G.: *Diabetes mellitus associated with chronic relapsing pancreatitis.* (Proc. Staff Meet. Mayo Clinic., V. 22, p. 553, Nov. 1947).

Between 1939 and 1945 there were 24 cases of diabetes associated with chronic relapsing pancreatitis, or approximately 0.3 per cent of the cases of diabetes mellitus, seen at the Mayo Clinic. In 15 cases symptoms of pancreatitis preceded the discovery of the diabetes by more than five years. Permanent diabetes makes its appearance only after a prolonged series of exacerbations each apparently involving greater portions (or more severely) of the pancreas. With flare-up of the pancreatitis the diabetes tends to become more severe, while with subsidence it is milder. When the external pancreatic secretion is affected so that the food absorbed is lower and malnutrition develops, the diabetes is ameliorated.

LAGERLÖF, H.: *Normal serum esterase and pancreatic lipase in diseases outside the liver, the biliary ducts and the pancreas.* (Acta. med. Scand., 128, 380, 1947).

Serum esterase and pancreatic lipase were determined in normal subjects and in patients with diseases other than those affecting liver, biliary ducts, or pancreas. While serum esterase was higher in value in normal men than in women, pancreatic lipase was of equal value in both sexes.

In 75 patients with various diseases the serum esterase and pancreatic lipase values were in most cases within normal limits. In some instances one of these was either higher or lower than the usual normal range but the other generally remained within normal range. It is interesting to note that in five

patients with diabetes mellitus not having clinical signs of other pancreatic dysfunction, the pancreatic lipase was low though the serum esterase was higher. In two patients with duodenal ulcer the serum esterase and pancreatic lipase values were both raised well above normal limits.

LIVER AND GALLBLADDER

RIGLER, LEO G. AND MIXER, HARRY W.: *Cholangiography and biliary regurgitation*. (Radiology 48,5463. May 1947).

The observation of the excretion of organic iodine compounds through the kidneys after injection into the biliary tract is recorded. Such excretion appears to occur uncommonly, being observed in eight cases out of a series of 460 cholangiograms. It is invariably associated with obstruction of the common bile duct.

The evidence indicates that the contrast medium finds its way into the blood by regurgitation through the liver. The phenomenon of biliary regurgitation is thus further established. It is probable that the reactions following cholangiography are due to a transient bacteremia rather than to distention of the bile ducts. In doing cholangiography, therefore, care must be exercised to keep the injection pressure low enough to avoid the danger of regurgitating bacteria or other foreign material into the blood.

FRANZ J. LUST

JONES, C. M. AND VOLWILER, W.: *Therapeutic considerations in subacute and chronic hepatitis*. (Med. Clin. North Amer., V. 31, p. 1059, 1947).

Laboratory data and symptoms frequently are inadequate to establish clearly the diagnosis and to evaluate the therapy employed. Liver biopsy, either by needle aspiration or by peritoneoscope, should be used to understand the exact nature of the liver pathology.

The numerous functions performed by the liver should be considered when the form of therapy is being considered. The diet should be high in calories and proteins. Since low fat diets are usually difficult to prepare or not palatable, a diet with moderate fat may be allowed providing the protein content is high. The vitamins to be included should be those for which there is either a specific need or an actual deficiency. Blood transfusion for anemia and intravenous dextrose for inadequate caloric intake should be used. Vitamin K should be given when the prothrombin concentration is low.

A long period of absolute bed rest, continued even when improvement is marked, is essential. Physical exertion and fatigue must be avoided.

The esophagus should be examined by X-ray at intervals to follow possible development of esophageal varices. These are due to portal hypertension and are poor prognostic signs in cirrhosis. Portal vein anastomosis to the vena cava may be considered

for relief of congestion. Sclerosing solution applied to the esophageal varices may be used to prevent hemorrhage.

ULCER

ZANE, M. D.: *Psychosomatic considerations in peptic ulcer*. (Psychosom. Med., Nov. Dec. 1947, V. 1X, No. 6).

The author finds that all ulcer patients have a definite type of complex, involving simultaneous feelings of fear and resentment. This "having to and fear of not being able to" or "must and can't" may be traceable in early life. The child seeks security by striving to meet rigid, exacting standards set up by the "early authoritative figure," while at the same time anticipating failure because of a strong feeling of inadequacy. It is characteristic of ulcer patients to strive forever to attain some goal notwithstanding difficulties which most men consider insurmountable. The author finds that ulcer activity and hypersecretion parallel psychological tension. Not all individuals possessing this type of tension due to this specific kind of conflict develop ulcer. Chronic ulcers heal as rapidly as acute ulcers when the conflict situation is removed.

HARKINS, H. N.: *The present status of vagotomy in surgical treatment of peptic ulcer*. (Northwest Med., Dec. 1947, V. 46, No. 12, 945-958).

In experiments, vagotomy reduces the incidence of marginal ulcers in Mann-Williamson dogs. In a series of 67 clinical cases, best results were obtained in cases subjected to vagotomy plus either stoma or resection. Vagotomy alone gave poor results, with gastroplegia, recurrence and diarrhoea as the chief complications. The author thinks vagotomy may be indicated in marginal ulcers and in patients with strong ulcer tendency or cases having had perforation, but he maintains a strong belief in the superiority of gastric resection.

SZASZ, T. S., LEVIN, E., KIRSNER, J. B., AND PALMER, W. L.: *The role of hostility in the pathogenesis of peptic ulcer: theoretical considerations with the report of a case*. (Psychosomatic Med., Sept. — Oct. 1947, V. IX, No. 5, 331-336).

The case is detailed of a young man with a duodenal ulcer whose anger (hostility) when marked, produced a tremendous hypersecretion of gastric juice, which even occurred in spite of the fact that all gastric secretion had been stopped by the administration of enterogastrene. This hypersecretive response to anger did not occur after both vagi had been severed below the diaphragm. Crying ordinarily gave the patient relief from the "lump in his stomach" which resulted from or accompanied anger. "Regressive innervation" is the recapitulation of an infantile pattern of physiological responses to certain emotional stimuli mediated by nervous pathways. In the infant, anger (crying) results in its being fed and the accompanying expectation of receiving food brings

about gastric secretion. Fear (that he might not be fed) would, on the other hand, do away with such a preparatory gastric secretion. The hostility (anger) in this patient is traced, on deeper psychological levels, to his early life, when as the favorite son of a hard-working but penurious mother, he received most of his happiness through oral aggression and weighed 40 pounds at the termination of breast feeding at about 10 months of age. The patient's hostility, as an adult, almost certainly was an important factor, among all the possible factors, in producing a peptic ulcer.

RIVERS, A. B.: *The syndrome of peptic ulcer perforating to the pancreas: a preliminary report.* (Proc. Staff Meet. Mayo Clinic, July 23, 1947, V. 22, No. 15, 290-296).

Careful evaluation of the signs and symptoms exhibited by patients who have peptic ulcer perforating to the pancreas generally makes it possible to recognize this complication without difficulty. Surgical, as opposed to medical treatment, is required. The article outlines the points of somatic reference of pain, depending on the structures involved by the perforating process.

SURGERY

DONALD J. M.: *Pre-operative and post-operative supportive therapy in gastro-intestinal surgery.* (Texas State J. Med., January 1948, V. XLIII, No. 9, 562-567).

While this article embraces much more, only the phase of nutrition is reviewed. The average patient requiring abdominal surgery does not present the problem of malnutrition. But it may become a real problem in patients with extensive liver damage, in high obstruction, and in the presence of a high intestinal fistula. A high caloric diet rich in protein and carbohydrates should be used in these patients. Oral or tube feedings are preferable. Sometimes intravenous alimentation in the form of glucose, amino-acid preparations, plasma and blood becomes necessary. Plasma is an excellent form of protein replacement but large quantities are necessary to furnish an adequate protein intake.

THOREK, P.: *Surgical treatment for carcinoma of the esophagus.* (Illinois Med. J., Dec. 1947, V. 92, No. 6, 329-337).

Cancer involving the mid-thoracic esophagus (zone 2) is best handled by transthoracic partial esophagectomy and partial gastrectomy with a supra-aortic esophagogastric anastomoses. Lesions in the lower esophagus and cardiac end of the stomach are best resected by a combined thoracolaparotomy incision which does not necessitate the removal of any ribs.

With the advent of positive pressure anesthesia in the hands of qualified anesthetists, chemotherapeutic agents, expert pre and post-operative care and the perfection of surgical technique, such extirpations are made possible, thus providing a new lease on life for these patients who only a few years ago were considered doomed.

PEMBERTON, J. DE J.: *The effect of chemotherapy on surgery of malignant lesions of the colon.* (Proc. Staff Meet. Mayo Clinic, Dec. 10, 1947, 561-565).

Other than the introduction of chemotherapy (chiefly sulfasuxidine and penicillin) there has been no major change in the management of colonic and rectal lesions during the past 12 years at the Mayo Clinic. Prior to 1939 when sulfonamides first were used, the hospital mortality in these cases varied 15 to 20 per cent. A slight decrease occurred in 1939, while in 1940 (when the sulfonamides were used more regularly) there was a decrease in mortality to five per cent where the rate has since remained. During this time, the proportion of diagnosed cases operated has increased as well as the proportion of operated cases resected. The incidence of fatal pulmonary embolism has decreased 50 per cent. Just as iodine therapy increased the safety of thyroid resection, so chemotherapy has increased the safety of resection for colonic and rectal cancer, but it must be realized that neither chemotherapy nor iodine therapy are substitutes for sound surgery.

ASHLEY, L. B. AND BENSON, C. D.: *Mesenteric vascular occlusion (four resected cases with three recoveries).* (Harper Hosp. Bull., Dec. 1947, V. 5, No. 6, 159-165).

The signs of mesenteric thrombosis or embolism are severe abdominal pain, vomiting, tenderness, usually rigidity and distention, rapid pulse, leucocytosis and shock. A flat film of the abdomen often shows the pattern of mechanical intestinal obstruction. It is probably the most serious abdominal condition, requiring surgical intervention for survival. With liberal use of heparin and antibiotics, adequate blood replacement and sound surgical treatment, the prognosis for this desperately ill group of patients is much brighter than ever before.

HUME, J. B. AND BLACKBURN, G.: *Synchronous combined total gastrectomy.* (Brit. Med. J., Nov. 22, 1947, 817-819).

The introduction of transthoracic total gastrectomy in 1938 was the beginning of a new era in the surgery of gastric cancer, but the immediate mortality still is too high and it is suggested that the quicker operation of thoracolaparotomy will greatly reduce this mortality.

The Effect of Insulin on Motility of the Stomach following Bilateral Vagotomy *

By

MAURICE FELDMAN, M.D.

and

SAMUEL MORRISON, M.D.

BALTIMORE, MARYLAND

IT HAS LONG BEEN KNOWN that insulin is a stimulant to gastric motility. Quigley et al. showed that insulin increases gastric motility in the normal and splanchnicotomized animal and inhibits motility following vagotomy. Lalich et al. also studied the effect of insulin on gastric motility, have likewise shown that motility is inhibited following vagotomy. They believe that the normal stimulating effect of insulin on gastric motility is through the vagal centers and that inhibition of gastric motility becomes apparent only with elimination of abdominal vagal stimulation. Hollander, more recently, described a physiologic test for the presence of uncut vagus nerve fibers following vagotomy. This test is based on the production of a hypoglycemia. A fractional gastric analysis is carried out to determine whether the resulting vagal stimuli, that are set up centrally, are able to evoke any secretory response of the stomach. A positive response to the insulin test, consisting of a rise in the curve of free acid of the gastric aspirates, accompanying the production of an adequate hypoglycemia, indicates that some uncut parasympathetic fibers are intact. However, a negative response is strongly suggestive, but not necessarily proof, that all the vagal fibers which pass into the stomach have been interrupted.

In our experimental problem, an effort was made to develop a test for vagotomy which did not entail any procedures, such as blood sugar tests and gastric analyses. We thought that a more simplified test would be informative regarding the effectiveness of vagotomy. With the knowledge of previous work and study of the action of insulin on gastric motility the development of a roentgen test might aid in simplifying the problem for the determination of vagotomy.

Five dogs were utilized for the normal gastric motility experiments. The fluoroscopic examination of these animals made five hours after the injection of 20 units of regular insulin showed a complete emptying of the stomach, with all of the barium in the large

intestine. This finding indicated a rapid motility and transit of the barium through the gastrointestinal tract.

THE EFFECT OF INSULIN ON THE VAGOTOMIZED DOGS

Fifteen experiments were done on five bilaterally sub-diaphragmatic vagotomized dogs. Twenty units of regular insulin were injected subcutaneously, and X-ray studies were made five hours after the administration of barium. It was interesting to note that not only was there a greater inhibition of gastric motility, but the stomachs in all of the animals showed a larger gastric retention and greater dilatation than before the administration of insulin. These findings were repeatedly observed, and so definite that the determination of the presence of vagotomy was striking. Furthermore, not only is the gastric motility increasingly inhibited, but there is considerable loss of tone with resulting greater dilatation following the injection of insulin.

CONCLUSIONS

These experiments show the following effects of insulin on the motility of the stomach.

1. In the normal animal the administration of insulin accelerates the motility of the stomach.
2. In the bilaterally vagotomized animal there is a greater inhibition of gastric motility, exceeding that observed after bilateral vagotomy without insulin.
3. In addition to the gastric motility inhibition, insulin further diminishes the gastric tone and causes an increased gastric retention and greater dilatation of the stomach than that observed following bilateral vagotomy without insulin.
4. It would appear that the effects of insulin are mediated through the vagus nerves.

Finally, it is suggested that on the basis of the data presented, a roentgen insulin test for the determination of vagotomy could be developed.

* Addendum: The above insulin test was carried out in two human cases, on whom a bilateral subdiaphragmatic vagotomy had been done. One case, showed a large five and a small 24 hour gastric retention. In the other there was no five or 24 hour gastric retention. Subcutaneous injection of 40 units of regular insulin did not have any noticeable effect upon the motility of the stomach as had been noted in dogs. The explanation for this difference is not clear at this time.

* From the University of Maryland, School of Medicine, Department of Gastroenterology.

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Dysentery, Colitis and Diarrhoea in Japanese Civilian Prison Camps in the Philippines during World War II. II: The Secondary Colites--- Post-Dysenteric and Non-Dysenteric. Animal Parasites.

By

FRANK G. HAUGHWOUT*

NEW YORK CITY

A GENERAL DISCUSSION of chronic colitis may very easily lead one into very deep water. Accordingly, I shall limit myself in this paper, to an account of colitis as we encountered it in the Philippine prison camps. The colitis we saw there, did not differ in any essential detail from colitis as I have studied it before and since the war; but in the camps, we had a large number of cases that could be studied under conditions of constant observation. We actually saw secondary colites develop from primary dysenteries and run their courses. Non-specific and idiopathic colitis are seductive terms with which to conjure, but I shall leave the problems they offer to others and review some very concrete situations that presented themselves to us every one of those thousand and more days and nights of our imprisonment.

Let me first briefly discuss some of the outstanding physical features of secondary colitis that contribute to confusion in dealing with this troublesome condition and bring embarrassment to the attending physician.

Colitis, in the strict sense, is an inflammatory condition and the tissues affected react in the manner characteristic of infectious inflammatory processes. However, unless the involvement is deep and extensive, patients suffering from a well-established chronic colitis seldom have an elevation of temperature. A rise of temperature in such a patient always should raise suspicion of a recurrence of the primary dysentery or some intercurrent condition unrelated to the colitis.

Chronic colitis seldom develops a fulminant exacerbation unless it has been allowed to get completely out of hand. As before, urgent symptoms suggest a recurrence of the primary dysentery or some complicating process. It usually is easy to define the situation; but diagnosis may be missed if it is assumed that the acute symptoms represent merely a "lighting up" or intensification of the chronic process.

A long period of time, perhaps years, may elapse before a small and indolent, but inexorably extending ulceration causes symptoms that will send the patient to his physician. By this time, it may be exceedingly difficult, if not impossible, to determine the origin of the colitis. An attack of dysentery in the past, may have been forgotten by the patient, or it may have been so mild and transient that it was not recognized as dysentery either by the patient or his physician.

In the prison camps we were able directly to trace most of our post-dysenteric colitis to the primary dysentery that provided the lesions for secondary invasion. This

experience has confirmed me in the belief I have long held, that much post-dysenteric colitis is preventable. Moreover, I hold strongly to the belief that most chronic colitis is born of dysentery — usually of the bacillary type.

From this point of view, the clinician would be well advised to consider every primary dysentery as likely to develop a post-dysenteric colitis. The obvious way to meet this issue is early accurate diagnosis of the primary condition and immediate, adequate and sustained treatment under microscope control. In the first paper in this series (1), I have outlined the general pathology of the dysenteries and now, by way of opening our discussion of the colites, I shall quote two more of the fundamental principles or axioms upon which the microscopical diagnosis of the diarrhoeal disorders is based:

7. All the infectious processes, including those which are not primarily inflammatory, sooner or later give rise to an inflammatory reaction that is readily detected through the microscope. In the bacillary dysenteries, the reaction is immediate and intense. In protozoal or helminthal dysentery, it comes later as a secondary bacterial involvement of lesions already produced by the proteolytic or mechanical activities of the parasites. Plus, of course, forms the background of these varied pictures. It always should be borne in mind that both its cytological characters and the quantitative proportion it bears to the other elements composing the bowel discharges, are of prime significance and, accordingly, of great importance in final interpretation.

8. Absence of inflammatory reaction for a period of five or six hours from the onset of an acute diarrhoeal disturbance, is an almost certain indication that the disturbance is not of an inflammatory nature. It is assumed, of course, that every successive bowel movement has been carefully studied and that note has been made of all evidence that may determine the true nature of the process. This is most important, for in the very acute enteric processes, the bowel is likely to be very quickly swept clear of much evidence that might have been used in making a diagnosis.

Dysentery, in the strict sense, is frankly honest in that it comes out in the open with a clear cut cellular picture that can be mistaken for nothing else by the experienced microscopist. But it must not be forgotten that many bacillary dysenteries of the paradysenteric (Flexner) type run a mild, evanescent course. Often in such cases, the first intimation that it has occurred comes to the patient and his physician in the form of a secondary colitis. There must be many such cases in endemic regions, and they must contribute a heavy quota to the chronic colites of undetermined cause. Moreover, they doubtless play a part in maintaining endemicity through recurrent primary attacks. Some years ago, I stressed the role of these obscure colites in chronic semi-invaldism in the tropics (2). From a few observations made in this country,

* Late Consultant, U. S. Army Institute of Pathology.

Formerly Professor of Protozoology and Chief, Department of Parasitology, Graduate School of Tropical Medicine and Public Health, University of the Philippines; Chief, Section of Parasitology and Cellular Pathology, Bureau of Science, Manila, (Retired).

I am beginning to suspect that they may lie back of some of the extremely destructive colites for which ileostomy seems to afford the only relief. They were not recognized and intensively treated early enough.

From a practical viewpoint, chronic colitis may be allocated to two groups: 1. Post-dysenteric colitis arising from primary dysenteries of bacillary, protozoal or helminthal origins. 2. Non-dysenteric colitis arising from surgical conditions as neoplasm, fistula, fissure or extra-intestinal abscess draining into the bowel, or caused by corrosive drugs as mercury, or by foreign bodies that wound the mucosa as they pass through the intestine.

In post-dysenteric colitis, the stools are typically muco-purulent and contain varying amounts of faeces. Often, there is no diarrhoea in the strict sense. The stools may be formed and hard in the face of a very extensive chronic colitis. A severe diarrhoea supervening in the course of a chronic colitis always should awaken suspicion of the presence of a concurrent condition such as the recurrence of the primary process, or the development of a separate non-inflammatory process. In the experience of the author, such intercurrent acute exacerbations less often are the expression of the chronic colitis unless it has been allowed to get beyond control. It is important that the clinician should realize the possibilities of such a condition before assuming that the diarrhoea is a manifestation of the colitis.

Diarrhoeas occurring in the course of a chronic colitis are a frequent source of perplexity to the clinician, who may regard them merely as an intensification of the colitis. Stepping up the colitis treatment in such cases not only fails to cure the diarrhoea, it may even aggravate it. Intractable diarrhoeas occurring in the course of a chronic colitis always should be investigated microscopically. Often, it will be found that they are of fermentative or putrefactive origin. They may even be centered in the upper tract. Obviously, such disturbances are not part of the colitis. They may, however, adversely influence it through irritation of the lesions, excessive peristalsis or, perhaps more potently, by the lowering of nutrition which needs to be kept at a high level in colitis.

Recognition of this condition and the rational handling of it was, perhaps, the most important and difficult task that had to be performed in the intestinal clinics at Baguio and Manila. Our diarrhoeas were very wasteful of the elements of our exceedingly restricted diet. Every ounce of nutriment had to be utilized. It was our ability to recognize the dual condition, that spared these patients the depletion of their vitality by these concurrent diarrhoeas at a time when it was necessary to conserve their nutrition to the limit of our resources. I shall discuss this point further in the next paper.

In bacillary dysentery, secondary colitis probably begins with the first solution of continuity of the mucosa by the dysentery bacillus, but the reaction is masked by the overwhelming, spectacular exudate of

the dysentery. The first signs of the developing secondary colitis, in the general run of cases of bacillary dysentery, usually become evident, microscopically, about the end of the first week. The changes that take place in the cellular picture may be described as regressive. There is a steady decline in the number of endothelial macrophages, and a general improvement in the cytological picture. Toxic necrosis of cells becomes less and less marked, karyolysis ceases and the cytoplasmic structure becomes more and more normal. These changes are particularly conspicuous in the neutrophile leucocytes. Annular degeneration of the leucocyte nuclei is lost as the nuclei become richer in chromatin, and the formation of fat globules in the cytoplasm ceases. The pus cells are still fragile, however, and a striking feature of this stage is afforded by the streaking out of cell nuclei in the making of stained preparations of the exudate (Fig. 1). When this appears, one may conclude that the active dysenteric process is on the wane and that a secondary

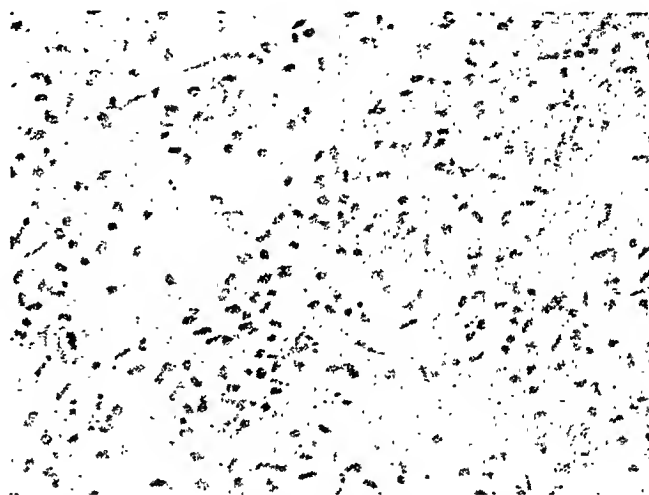


Figure 1. — Regressive cellular changes in subsiding bacillary dysentery. Note streaking out of leucocyte nuclei as they grow richer in chromatin.
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suppurative process is replacing it. The exudate then takes on the characters of a simple suppurative reaction. It retains these characters thenceforth, unless a recurrence of the primary process takes place. In that event, macrophages reappear, cell necrosis again becomes evident and the exudate quickly shows the cytological picture of acute bacillary dysentery. If the case has been kept under constant microscopical control these cellular changes are easily detected. Often they appear before there is any marked change in the clinical picture. Accordingly, prompt treatment may abort the recurrence before the patient becomes really ill again.

Once established, the exudate of secondary colitis is seen to be composed mainly of healthy looking pus cells. Epithelial cells are conspicuous; they occur singly and in blocks. If the lesion is above the rectal ampulla, these will be of the columnar type (Fig. 2). If it lies in the ano-rectal region, large numbers of squamous epithelial cells will be seen scattered among the pus

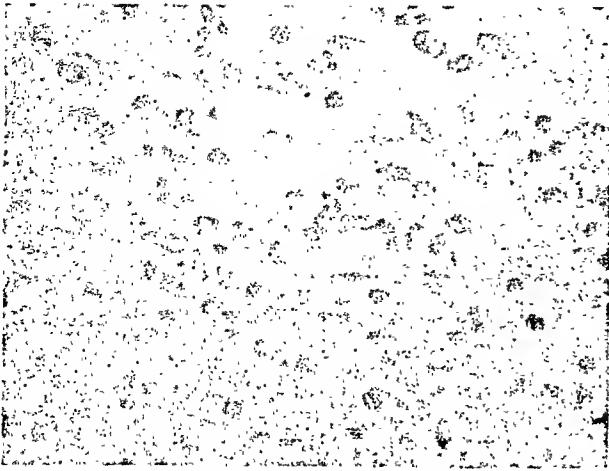


Figure 2. — Cell picture in established secondary colitis. Note columnar epithelial cells scattered among the leucocytes.

cells (Fig. 3). The stools usually are muco-faeculent and, in old cases, the mucus may be inspissated. There is little, if any, blood. The presence of epithelium, alone, in mucus usually means nothing more than simple erosion of the mucosa. The presence of pus cells is necessary to establish a diagnosis of colitis.

In protozoal and helminthal dysentery, secondary colitis begins with the solution of continuity of the mucosa *from within*. With the break through, tissue-dwelling forms, or trophozoites, of the amoebae appear in blood-streaked mucus. At first there are few tissue cells and leucocytes, and those present show evidence of proteolysis; the attack on the cells is at the periphery only, giving them the familiar "mouse eaten" appearance. This is strikingly seen in the neutrophile leucocytes which show varying degrees of destruction to the point where only the lobed nuclei remain, forming what are spoken of as "pyknotic bodies." These are characteristic of amoebic dysentery.

This scant exudate persists only a few hours. Inflammatory reaction arising from secondary bacterial invasion from the lumen, develops rapidly and by the second day the stool is markedly purulent through the infection that has spread into the submucosal cavity.

By this, it will be seen that amoebic dysenteries are not primarily inflammatory affairs, but that they always develop a secondary colitis. This may be very marked and become the most urgent factor in the condition. This is largely because, unlike bacillary dysentery, the secondarily invading bacteria find a pre-formed lesion deep in the submucosa. Anti-amoebic treatment may be pushed to an extreme without the slightest effect on the secondary infection. A separate bactericidal attack must be made on this secondary condition, but this, in turn will have no effect on the amoebic infection. In short, it will be seen that amoebic dysentery must be regarded as a double infection which must be dealt with accordingly, if the patient is to prosper. Intestinal schistosomiasis produces a

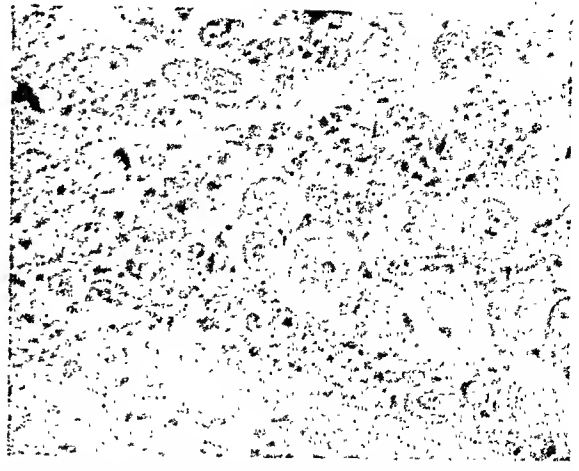


Figure 3. — Cell picture in secondary colitis localized in the ano-rectal region. The large cells are squamous epithelium.

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cellular reaction that is difficult to distinguish from that of amoebiasis. Similar treatment is indicated.

Therefore, it is seen that these post-dysenteric colites are endogenous infections. They differ little from each other in a qualitative sense; such differences as they may show in individual cases are quantitative and are in direct proportion to the extent of the primary lesion and the promptness and adequacy of the treatment.

Every primary dysentery, no matter what the type, is succeeded by a post dysenteric colitis of greater or lesser extent. I base this statement on the study of thousands of cases. If the patient is in a state of good nutrition and the primary access is mild and transient, complete healing may take place early if the treatment is adequate. However, this is not a thing upon which complete dependence may be placed. A circumscribed, low grade ulceration may persist for an indefinite period. The suspicions of the patient and his physician may not be aroused unless it involves larger areas of the bowel wall or burrows deeper. I have picked up countless cases of these symptomless colites in the routine search of stools for parasites. Often, I have had difficulty in convincing the attending physician that the condition was present. The situation becomes embarrassing if an endoscopist reports failure to find evidence of colitis.

In thoroughly competent hands, endoscopy is a most valuable adjunct in this work. In incompetent hands it may lead to serious error. There sometimes is failure to realize that it gives no clue to conditions above the sigmoid. The descending colon may show no lesions, but they may be present above the sigmoid. Moreover, a condition of hyperaemia of the mucosa may be interpreted as colitis without the realization that hyperaemia resulting from simple irritation of the mucosa by irritating substances in the faeces, with consequent simple catarrhal reaction, is exceedingly common. This was strikingly brought out in

our studies in the camps. Hyperaemia is *not* ulceration. In the strict sense, colitis implies ulceration with inflammatory reaction. These catarrhal cases do not respond to bactericidal treatment; they do far better on the discovery and removal of the cause of irritation.

When it is possible to secure an adequate amount of material and study of it can be made on the spot by an experienced man, much can be learned from a biopsy performed through the endoscope. However, such material too often is sent to the laboratory and examined by a technician who has no sound knowledge of cytology. Rarely, is it properly interpreted. Tissue cells frequently are mistaken for amoebae and a false diagnosis of amoebiasis is made.

I am showing (Fig. 4) a typical example of such a mistake in interpretation. The preparation was made from the stool of one of our Santo Tomas patients

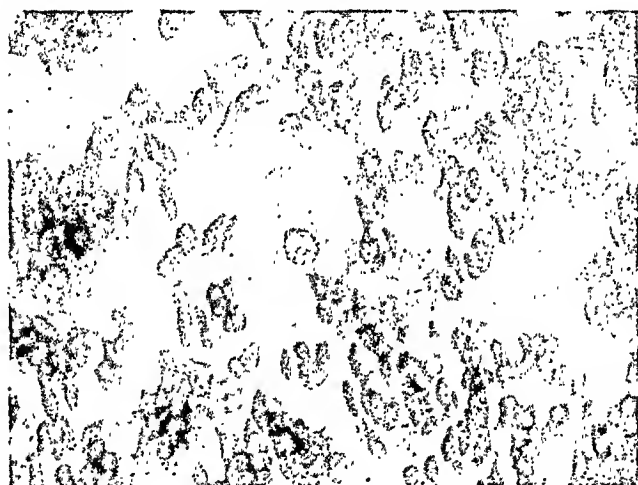


Figure 4. — Squamous epithelial cell in haemorrhagic stool of acute putrefactive diarrhoea. This cell was mistaken for *Endamoeba histolytica*, by a laboratory technician.

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who had been under treatment for a violent putrefactive diarrhoea following food intoxication. One morning, she passed a large quantity of blood and the stool was sent to one of the other camp laboratories. There, a diagnosis of amoebic dysentery was made on the discovery of cells like that shown in the figure which were thought to be *Endamoeba histolytica*.

Clearly, these cells were squamous epithelium as will be apparent from inspection of the figure. The laboratory technician brought the stool to me for confirmation of his diagnosis. I was able to convince him of his error. The stool also contained numerous motile *E. coli* which further contributed to his confusion. It will be noted that no pus or other cellular structures were present. The discharge consisted entirely of clotted blood, mucus and the cells I have mentioned. There was no basis for a diagnosis of dysentery of any type. As I shall show in the next paper in this series, one may find, in all catarrhal conditions of the bowel, cells that are difficult to distinguish from amoe-

bae unless one has a sound knowledge of protozoa and cytopathology. It is only necessary to recall that in the past, countless cases of bacillary dysentery have been labeled amoebic dysentery because microscopists have mistaken endothelial macrophages containing phagocytosed erythrocytes for *Endamoeba histolytica*.

In passing, I may remark that I cannot recall any case of genuine colitis that I have seen diagnosed endoscopically, that could not have been detected by thorough microscopical study. I have seen many, however, in which similar microscopical study has demonstrated error in the interpretation of the endoscopic findings.

The question often is asked what proportion of primary bacillary dysenteries may be expected to develop a chronic post-dysenteric colitis. I define a chronic colitis as one that persists more than a month after the onset of the dysentery that caused it. The plan of study in the prison camps included an inquiry into this. The question is difficult to answer except in general terms, for several factors are involved. I shall try to meet it by citing conclusions drawn from our observations in the camps.

Four of these factors may be regarded as fundamental; I list them in what I consider to be the order of their importance: 1. The time elapsing between the onset of symptoms of acute dysentery and the diagnosis and application of treatment. 2. The adequacy of the anti-dysenteric treatment. 3. The state of nutrition of the patient. 4. The virulence of the dysenteric infection. Delay or neglect easily may lead a mild dysentery into a tedious chronic colitis, while resolute and resourceful action on the part of the clinician may overcome the handicaps of lowered nutrition and a virulent infection. These things were shown many times in the camps. In other words, it is apparent that the best time to treat a post-dysenteric colitis is during the first days of the initial dysenteric attack. The patient responds far better to the preventive treatment than he does later, to the treatment directed against a well established secondary infection.

On reviewing my observations, not only in the prison camps, but prior to the war, I think I may venture to say of the general run of bacillary dysenteries of average severity, that of those that go wholly untreated, 80% may be expected to develop a chronic colitis; of those in which diagnosis has been delayed or treatment has been inadequate, 60% may be followed by chronic colitis, and in those in which diagnosis has been early and treatment prompt and adequate, the incidence of chronic colitis may be as low as 30% or thereabouts.

What may be accomplished by early diagnosis and prompt and adequate treatment was strikingly demonstrated in the camps in our studies of a group of persons who must be regarded as poor subjects for dysentery and its sequelae.

Up to January 1944, our sole means for the treatment of bacillary dysentery was magnesium or sodium

sulphate administered in aperient doses during the acute stage. This treatment promotes drainage from the inflamed areas, retards absorption and, unless overdone, is far better than no treatment at all. However, it does not appear to restrain the development of post-dysenteric colitis. Late in 1943, the Red Cross succeeded in getting a supply of sulfaguanidine and sulfathiazole into Santo Tomas Camp, but it was not released for use until March 1944. At that time about 85% of our cases of primary bacillary dysentery were developing post-dysenteric colitis.

Many of the camp physicians, outside of our clinic, were opposed to the use of sulfaguanidine. They told the internees that it was dangerous and inefficacious. In view of the fact that the strength and vitality of the prisoners were rapidly deteriorating, we decided, in March, to use the sulfa-drugs in the Intestinal Clinic. Good results immediately followed. We then started a campaign of education of our own. A steadily increasing number of patients braved the terrors that had been pictured to them. Their precept and example encouraged others and within a few weeks, nearly every one who came to us for treatment of dysentery asked for the drug. One after another of the camp physicians in other clinics began to administer it and by the Fall its use was practically universal in the camp.

By May 1944, the incidence of chronic post-dysenteric colitis in our clinic had fallen to 51%; by August it was down to 40% and the low point was reached in December with an incidence of 34%. The curve (Chart A) was, of course, irregular, but the fluctuations upwards from month to month never exceeded 8%. The downward trend was steady.

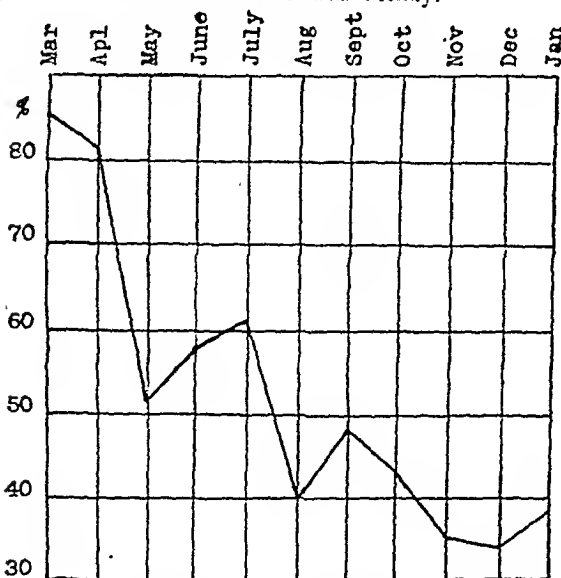


Chart A. — Incidence of post-dysenteric colitis under treatment with sulfaguanidine.

In appraising these figures, one should note that they are based on the study of patients with a primary bacillary dysentery. Their stools were studied at least once daily over a period of two months. Every one of them carried over a post-dysenteric colitis

after the subsidence of the acute dysentery. This is inevitable in every case of bacillary dysentery. The only question in such cases is: Will the colitis be transient or protracted? Only those in whom the colitis persisted for more than a month, do I classify as having a chronic colitis. Many of those who developed the chronic condition still suffered from it when they were repatriated in 1945. Doubtless, many of them still have it. This is one of the most important post-war conditions that will beset these people.

Nearly all the chronic colites observed in the prison camps obviously were of dysenteric origin. However, a few could not be attributed to that cause. Studies of these cases served to confirm more extensive observations made before the war. Unfortunately, the records and pathological material of these pre-war studies were stolen by the Japanese when they occupied Manila.

Often it is possible for an experienced microscopist to distinguish between a chronic colitis of dysenteric origin, and one that has arisen from another cause — a non-dysenteric colitis. He may not be able to state exactly what is the underlying cause, but by elimination, he can point the way to further investigation that may lead to its definition. Much may be gained if it can merely be stated that the process is not dysenteric. At least, the microscopist can give pause to any impulse to treat, let us say, an ulcerating carcinoma by the application of anti-dysenteric therapy. Always, he can state, with confidence, that the case is not acute dysentery. Elsewhere (3), I have discussed in detail, the cytological characters that, in most instances, distinguish non-dysenteric from post-dysenteric colitis. Briefly reviewing them here, we may note that the stools in these cases remain formed to somewhat loose unless some intercurrent condition develops. The exudate usually is creamy and sero-purulent. Seldom, if ever, is it mucoid to the extent that one sees mucus in dysenteric and post-dysenteric stools. Wet fixed and stained by proper technique, these exudates present a very characteristic appearance.

In the process of wet fixation, marked shrinkage of the serous portion of the exudate takes place so that when the preparation is stained with haematoxylin and eosin, the individual cells are seen to lie within a clear annular zone (Fig. 5). The effect is very striking. Rarely, this picture may be seen in extremely fulminant cases of dysentery in which there has been great destruction of the bowel wall with obliteration of the mucus secreting cells and massive secondary supuration. The stools in these cases are serous and very haemorrhagic — the so-called "meat washings stools." Such a condition seldom is encountered except in infections with the Shiga strain (*Shigella dysenteriae*) of the dysentery bacillus, or in old, neglected amoebic cases. I shall cite two cases of non-dysenteric colitis from our Santo Tomas records:

The first patient had long been under treatment for dysentery in one of the other camp clinics. Our first examination disclosed the cellular picture that has just been described (Fig. 5). Dysentery was immediately ex-

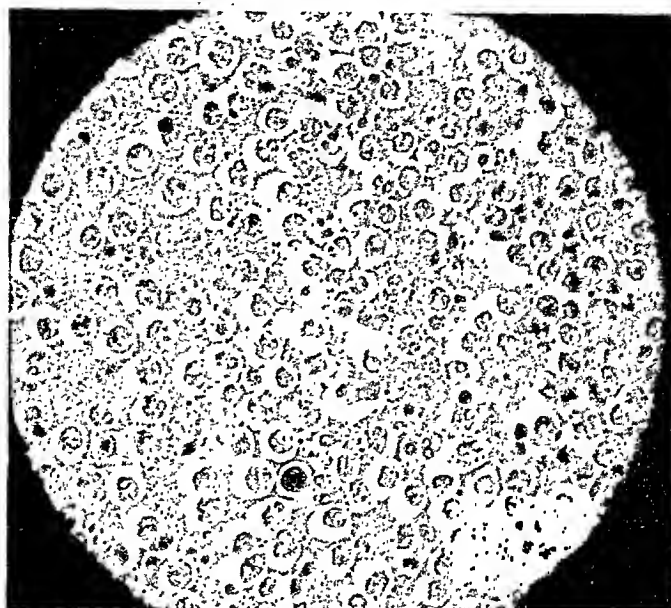


Figure 5. — Cell picture in ulcerative carcinoma of the colon. Note clear zones surrounding the cells in this serous exudate. Contrast with Figure 2.

cluded, but the case was studied for several days, during which it became clear that the process was suppurative. Certain cells suggested a possible malignancy. The patient was referred to the surgical staff with the recommendation that endoscopic study be made. A large, ulcerating tumor was found. At operation it was disclosed that the tumor was a carcinoma of the colon with extensive metastases. The condition was inoperable and the patient died soon after.

The other patient came to us complaining of pain in the right supra-pubic region. No pathology was found on repeated stool examination, but a mass was evident on abdominal palpation. Shortly afterward, this mass suddenly subsided with relief from the pain and the patient began to void a creamy, purulent exudate. Again, the exudate was of the sero-purulent type exhibited by the other patient. No experienced man would have mistaken it for the exudate of dysentery. Sulfathiazole was administered and the purulent discharge ceased in about two weeks. It seemed evident that it was the expression of an extra-intestinal abscess that had ruptured into the bowel. I have seen similar pictures in severe appendiceal abscess.

Such a case as this, of course, is not a colitis in the strict sense. There may be no lesion of the bowel except at the point of perforation where the inflammation may be completely localized — the absence of mucus would indicate this. But it presents a picture suggestive of non-dysenteric colitis — certainly not one of dysentery or a characteristic post-dysenteric colitis.

By way of summarizing our observations on post-dysenteric phenomena in the two camps, I present Table I.

TABLE I

Post-Dysenteric Phenomena: Percent Recapitulation.

	Baguio	Manila	Average
Post-dysenteric colitis	62.2%	49.4%	55.8%
Acute recurrence	33.7	31.7	32.7
Cases recurring not more than twice	78.4	83.2	80.8
Recurrence within first two months	68.7	55.0	61.8

The averages need not necessarily be accepted as standard figures; but they may be regarded as showing probable incidence rates. At least, they convey something more than a vague hint that much is gained by getting immediate control of a dysentery and maintaining that control.

INTESTINAL ANIMAL PARASITES

Before concluding our discussion of the infectious processes in the prison camps, it would seem appropriate to say something regarding intestinal animal parasitism. While the statement doubtless will surprise many readers of this paper, truth compels me to state that at no time did intestinal animal parasites offer a serious medical problem in the camps. The only real trouble arose from ill-advised, often unwarranted treatment against light (sometimes non-existent) infestations. Sometimes these ill directed efforts were attended by serious consequences. The incidence of pathogenic species was low. That of the nematode *Ascaris lumbricoides* with which 156 persons were found to be infested, was the highest of any individual parasite. No individual was found to harbor more than four ascarids. Only twenty-one cases of infection with *Endamoeba histolytica* were recorded. They have been discussed in my first paper (1). The parasitological findings in both camps are tabulated (Table II).

The question naturally arises as to how thoroughly the search for parasites was conducted. All the microscopy in our clinics was done by the writer and in the course of these studies he examined more than 20,000 stools. This work was done in addition to my other duties which lay in studying and advising patients, consultations and the outlining of treatment with the other members of the medical staff of the clinic, and keeping the records. This occupied my time daily for

TABLE II

Incidence of Parasitism in Baguio and Manila.

	Baguio	Manila	Total
<i>E. histolytica</i>	5	16	21
<i>E. coli</i>	63	70	133
<i>Trichomonas</i>	6	40	46
<i>Chilomastix</i>	1	25	26
<i>Giardia</i>	6	27	33
Hookworm	2	1	4
<i>Ascaris</i>	24	132	156
<i>Trichocephalus</i>	7	15	22
<i>Enterobius</i>	0	12	12

from 12 to 18 hours aside from night calls. On light days, from ten to 25 stools were handled, but there were many days when from 40 to 60 or more stools were studied. The conditions called for rapid and accurate work; it was not a job for amateurs. Calculations show that an average of fifteen minutes were spent on each stool. Much can be accomplished in that time by an experienced worker. Special examinations for parasites were not made unless there was definite indication of their necessity. Lack of reagents and apparatus made it impossible to do stool concentrations. Accordingly, nearly all cases of parasitism were picked up in the course of the study of the stools of persons who were definitely ill. For instance: We detected parasites in 102 persons or 20.4% of the Baguio camp population. Of these infestations, nearly 40% were discovered the first time the individual's stool was examined. Table III will give an idea of the distribution of the findings.

TABLE III

Detection of Parasitism in the Baguio Camps

Examination	First	Second	Third	Fourth	Fifth
Number detected	40	14	8	10	7

In short, we picked up 77.4% of our parasitized patients within five stool examinations. From then on, the detection rate fell rapidly. In instances we did not find parasites in an individual until his stool had been examined twenty or more times. The stools of some patients were studied on more than 150 occasions. One patient received forty-two stool examinations before ova were found. This suggests the assumption that most of our patients brought their parasites into camp with them and that infestations acquired in the camps were small in number.

In Santo Tomas Camp, the incidence of animal parasitism was found to be 23.7% which is close to the Baguio figure.

Little need be said about these figures for they do not differ essentially from peace-time figures in the urban American and foreign groups in the Far East. Native incidence always is much higher in tropical countries. We probably missed some protozoan infestations because on busy days stools often stood for a considerable time before they could be examined. The obviously acute cases always received first attention. This probably accounts for the low figures on the flagellates and small amoebs; it would not affect the findings of encysted amoebs or other protozoa. I cannot account for the low incidence of *Trichocephalus*.

We detected no *Enterobius* infestations in Baguio, but recorded twelve in the laboratory at Santo Tomas, eleven of which occurred in children. However, *Enterobius* was epidemic among the children in Santo Tomas. Most of the diagnoses were made by the mothers.

True to tradition, many lay and medical inmates of the camps attributed a large amount of the intestinal disease to "worms." Much "worm medicine" was administered without any previous laboratory diagnosis. The prevailing hyper-sensitiveness of the intestinal mucosa made this a dangerous procedure. I shall offer evidence of this in the next paper. We ceased giving anthelmintics in the Intestinal Clinic early in 1944 after we had convinced ourselves that they caused more harm than could be attributed to the "worms."

We also discontinued the administration of cathartics for the same reason. A dose of salts that under normal conditions would have spent itself in a few hours, in the last days of the camp, set up an intestinal tumult that lasted many days and was very weakening to the patient. When it was imperatively necessary to move the bowels, we gave common salt in hot water — one heaping teaspoon of salt to a glass, three glasses being given to an adult. It was effective, produced little if any irritation and, we thought, helped to restore a chloride balance in severe diarrhoea.

We studied the cases of a number of prisoners who were made very ill by hexylresorcinol and purgatives administered by persons not connected with our clinic. Hyper-sensitive bowels reacted to this treatment with violent and prolonged diarrhoea with blood-stained stools. The catarrhal reaction was intense. Often, there were severe pain and prostration which persisted for days. I recall, in particular, two children and one adult who were treated with hexylresorcinol in another clinic. Eventually, they were brought to our clinic with severe dysenteriform symptoms. All were very ill for several days. Summing up the evidence, we found the net results of these treatments to be: Three patients with hyper-irritation of the intestine, previously acquired, made violently ill by the treatment. One patient voided an adult *Ascaris*: the others produced none. Repeated search of the stools of all three failed to disclose any ova of *Ascaris* or other helminth. In no case had the stools been examined prior to treatment. These three cases were quite typical of others we saw.

In forming an opinion, from the foregoing, as to the possible ill effects on the patient of hexylresorcinol, the reader must bear in mind that the intestines of these patients were in a state of marked irritation before the drug was given. They were not normal intestines.

There is no doubt of the important role that certain animal parasites play in intestinal pathology, or of the great harm they work in the native populations of tropical and sub-tropical countries who usually harbor massive infestations. But it is a great mistake to apply the figures for these native races to lightly

infested urban Caucasian groups who live on a far higher sanitary plane than do the natives. The sanitary conditions in the prison camps, bad as they were at times, were not favorable to the dissemination of helminthal infection. This seems to have been shown by their incidence in the camps which was about the same as would be expected in any Caucasian group in the Far East.

In the next and concluding article, I shall deal with the so-called "functional diarrhoeas." In these conditions the cellular response of the bowei wall is radically different from the responses we have so far discussed, and clearly places this group of disturbances in a separate category. The earmarks of this catarrhal response to irritation, as distinguished from infection and inflammation, form a prime factor in differential diagnosis.

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Anterior Pituitary and Pancreas

By

JOSEPH WILDER, M.D.

NEW YORK, N. Y.

OUR CONCEPTS ABOUT THE ROLE of the pituitary gland in the metabolism of carbohydrates have been subject to considerable change in the last few years. The "Houssay dog" and the "Young diabetes" became classical concepts of experimental medicine just as the "Pawlow dog" had been a few decades ago. The latest developments concerning the role of the pituitary in the sugar metabolism have surpassed even the expectations of those few who had advocated this idea in the past.

While the old students of diabetes (v. Noorden, Falta, etc.) held the view that the pituitary does not play any important role in the sugar metabolism, Lichtwitz and others were not so sure of that. In 1930, in a comprehensive survey of the relations between the central nervous system and sugar metabolism we did not dare express more than this conclusion: "there is hardly any doubt that the anterior pituitary exerts a stimulating influence on the sugar metabolism although it is impossible to state how far this influence extends under normal conditions" (228). Compare with this the blunt statement by Houssay (101) in 1933: "the pituitary is a main organ of the carbohydrate metabolism alongside with the pancreas or liver;" or Joslin's more cautious conclusion in 1937 (111): "an evergrowing body of experimental data points to the profound influence of the pituitary gland on the carbohydrate and fat metabolism."

However, for the critical observer the great amount of data collected still appears partly contradictory and confusing. The same is true for the variety of

theories in this field. This survey was undertaken with the hope of arriving at a concept reconciling and covering more of the controversial data than was possible until now.

REMOVAL OF THE ANTERIOR PITUITARY AND THE CARBOHYDRATES

It has now been established that the removal of the anterior pituitary in most animals (including rats) leads to a drop in blood sugar level after a brief transitory (2-3 days) period of hyperglycemia and glycosuria. This slight or severe hypoglycemia could be observed for months.

The "pituitary hypoglycemia" is not very different from hypoglycemia of other origin. One of its characteristics seems to be that it becomes manifest especially after fasting. Another characteristic feature is apparently a special oversensitivity to insulin so that even very small doses may prove to be fatal (literature in 221). Compared with these two features other data are less important. All these effects can be abolished by implantation of the pituitary gland or by injection of proper pituitary extracts.

One of the most interesting series of observations is credited to Houssay and his co-workers: the abolition or prevention of pancreas diabetes by hypophysectomy and its return after transplantation of hypophysis or injection of proper pituitary extracts.

We have almost no opportunity for the counter-experiment of artificial hyperplasia or hyperfunction of the pituitary. Injections of gland extracts are not

a full substitute. The normal organism shows a remarkable lack of response or resistance to those preparations. This is the reason why we have to recur to removing the gland, producing symptoms of deficiency and often consecutive anatomical changes in various organs and then watch these changes disappear under the influence of gland extracts. The conclusions from such experiments have to be taken with a grain of salt especially in the case of hypophysis in which we are still dealing largely with non-purified extracts.

EXTRACTS OF THE ANTERIOR PITUITARY AND THE CARBOHYDRATES

Some purposeful incompleteness is necessary in reviewing the tremendous amount of observations for the sake of better understanding. It can be stated in general that the extracts of the anterior pituitary lobe increase the metabolism of carbohydrates, raise the level of blood sugar, decrease the tolerance for carbohydrates, depress the insulin- and increase the adrenalin-effect on the blood sugar. All these effects are not very outspoken in normal, more marked in hypophysectomized animals and easy to demonstrate on Houssay's pancreatectomized animals (107, 151). There are great variations in various species but this is true also for the pancreas-diabetes which is easy to produce in some, hard in other species. It is a climax to those studies that Young (102, 195, 221) and his co-workers preceded by certain experiments by Johns (114a) and Evans, succeeded in producing permanent diabetes in normal dogs by daily injections of large amounts of pituitary extracts. These experiments could not be duplicated in other normal animals but Lukens and Dohan repeated this experiment in pancreatectomized cats (153), etc. The "Young diabetes" has most features of ordinary pancreas-diabetes but seems to show a few interesting differences like greater resistance to insulin, no change in the glycogen content of the liver, no loss of weight etc.

These experiments have not yet been duplicated in man although single cases are noteworthy like that of a young man in whom permanent diabetes has been produced by injections of a "pituitary anterior like substance" ineffective in rabbits (224). The opposite case is that of a diabetic with retarded growth and sex development whose diabetes was improved by injections of growth hormone (37a).

Thus Young and others have arrived at a concept of a "diabetogenic hormone" of the anterior pituitary. One statement should be made right here and then: all the diabetogenic effects of the anterior pituitary extracts have been achieved by very crude extracts showing also properties of growth promotion (e. g. 150). Meanwhile a number of separate hormones of the anterior pituitary have been "discovered" most of them claiming some relation to the carbohydrate metabolism. Without going into details we want to present here the summary of our study of the vast literature on this subject.

The *adrenotropic* (corticotropic) hormone is not diabetogenic (105) but it is to a certain extent an antagonist of insulin (80); restores in the rat the changes in carbohydrate metabolism following hypophysectomy (192); has some controversial effect on the glycogen of the liver (113, 169). It has properties of a *growth hormone* (30, 221). Collip (34) says that its task is the maintenance of the adrenal cortex in *morphological* as well as functional sense.

The *thyrotropic* hormone has only some controversial effects on the blood sugar (144a, 151, 243, 171) and on the liver glycogen (195, 169, 171, 151). It is not diabetogenic and has no effect on the pancreas diabetes (151). It does not affect the insulin resistance (113), is not ketogenic (30). It is difficult to separate from the diabetogenic and hence also from the *growth hormone* (243).

The *gonadotropic* hormone is not diabetogenic (144a) and perhaps not metabolic at all (151). It has no influence on the blood sugar (30, 45, 105, 151, 133) and does not counteract the *cachexia* in Simmond's disease. Its only much contested relation to the sugar metabolism is its reported beneficial effect in certain cases of diabetes in the menopause (112, 198).

Prolactin is not diabetogenic (192, 169), does not influence insulin resistance (113). If it sometimes shows some hyperglycemic effect we must not forget that it often contains certain amounts of diabetogenic hormone (244) with which it is closely associated (243).

The existence of a *parathyreotropic* hormone is yet doubtful, its relation to the sugar metabolism is but little known (31, 243).

In contrast to those fractions *growth hormone* is diabetogenic in normal as well as hypophysectomized animals (144a, 30, 101). Its effect parallels that of diabetogenic hormone (144a, 221): it shows the same period of latency in mammals as the diabetogenic hormone has (101). It is an antagonist of insulin, aggravates pancreas diabetes and phlorhizin diabetes, etc.

We have had lately the opportunity to treat a case of severe chronic hypoglycemia of unknown origin in a psychosis of two years duration with a commercial preparation called "growth hormone." We have had experience in the past with treatment of pituitary hypoglycemia with various kinds of anterior pituitary extracts and have been an early advocate of crude preparations (praeparation) for that purpose (229, 230). We have been struck though by the effectiveness of this extract in improving both the blood sugar level and the psychotic symptoms. We could also notice in this case a number of analogies to Young diabetes in dogs, namely an initial period of latency and a later refractory period accompanied by clinical and metabolic relapse and necessitating an increase in dosage.

In addition to diabetogenic hormone a number of other pituitary substances have been described by various authors as separate hormones of sugar metabolism: *pancreatropic* (6, 7, 170, 58, 238, 151, 50), *glycolytic*, *glycolytic* and *hyperglycemic* factors. To these we may add substances isolated from blood and

urine of patients with diabetes or acromegaly and animals injected with anterior pituitary extracts. Finally the ketogenic hormone, indirectly connected with sugar metabolism, may be included here. The mass of experimental data in this field is mounting daily but many conclusions reached are still controversial. Thus Collip acknowledges only two hormones of sugar metabolism, Young (245) three, Evans (51) five and Bomskov (19) seven. We are compelled to omit in this Chapter references to the vast literature which has been surveyed several times by more competent authors (77, 221, 106, 63, 90, 30, 194, 12, 67, 153, 46, 68, 62). We do not discuss the "glycostatic factor" not firmly established in man (23a, 28) which is said to act on the muscles of hypophysectomized animals. Neither do we discuss the "glycolytic factor" Anselmino's and Hoffmann's. We shall rather present directly the conclusions to which we have arrived after having studied this literature.

Four substances have been described as special and direct pituitary hormones of carbohydrate metabolism: 1. diabetogenic (Young); 2. pancreatropic (Anselmino and Hoffmann); 3. glycotropic (Young) and 4. hyperglycemic (Anselmino and Hoffman). All these hormones are derived in the last instance from dry powders, mostly acetone dried, of the pituitary gland of various species and are thus related more or less closely to the growth and diabetogenic hormone (51). The important feature in the establishment of the diabetogenic hormone was the discovery that it was very thermolabile and must be produced in low temperature. The latter is true also for the pancreatropic hormone while the other factors are more thermostabile. Other points of difference are: diabetogenic hormone is alkaline, pancreatropic has an effect at a range of pH 5.3 to 9.4; the hyperglycemic factor is boiled at 5.3. The diabetogenic and pancreatropic factors become ineffective by addition of stronger acids or alkalis. There are no differences in the solubility in various media and the main difference between the diabetogenic extract and the other is that the diabetogenic loses its effectiveness by ultrafiltration. In contrast to the pancreatropic hormone it is easily absorbed by various substances. We think it is right to say that we are dealing in all cases with growth (diabetogenic) hormone partly altered in its properties by heating, ultrafiltration or changes in pH. Whether these alterations are ever duplicated by nature we do not know. Diabetogenic as well as growth hormone seem to occur in amphibians and mammals only (77).

Considering in the same way these carbohydrate hormones s. str. together with other hormones of the pituitary (197, 77, 51), we would come to the following conclusions: growth and diabetogenic hormones are associated, possibly even identical.*

* In 1944, Young (246) himself supplied the best illustration of this relationship; the same extract which causes growth without diabetes in puppies, causes diabetes without growth in adult dogs. In one adult dog, however, diabetes did not develop and growth continued; in this animal the thyroid became enlarged and the islets of the pancreas showed hyperplasia instead of the usual hypoplastic degeneration.

All the other hormones of the hypophysis still show a rather close association with the growth hormone and by the same token with diabetogenic hormone. Only the gonadotropic factor seems to be an exception; this is also the hormone which in its purified form shows the least relation to the metabolism of carbohydrates (221). The gonads seem to hold a special position in their relation to the hypophysis as will be shown later in this paper: hyper- and hypo-function of the pituitary does not affect them in opposite ways as it does other glands; they show atrophy in both acromegaly and Simmond's cachexia. We are therefore satisfied that there are only two hormones of the anterior pituitary: the gonadotropic and the growth hormone. The latter can be altered in various ways so as to exert incomplete, partial or paradoxical effects, trophic as well as functional (tropic). Those partial effects have been identified in the literature with separate hormones. In its functional effects as far as sugar metabolism is concerned the diabetogenic hormone has all the properties of those other "hormones" but not vice versa. This is true for blood and urine sugar, ketone bodies, glycogen of liver and muscles, insulin and adrenalin effect, etc. In order to come to this conclusion one must strongly keep in mind that every inhibiting agent may have a stimulating effect under changed circumstances; this depends not only on the dosis but also on the condition of the effector organ (susceptibility), chronic or momentary. The same extract under different circumstances may raise or lower the blood sugar level, replenish or deplete glycogen reserves, damage or stimulate the islet cells in their development, etc. We have elaborated on this in the past in several papers on what we call the "law of initial values" (235). Applied to the diabetogenic hormone this law would mean that the diabetogenic hormone has an effect contrary to insulin only under certain circumstances. We do not know exactly how important this effect is under average conditions. According to the "law of initial values" a certain dosis of diabetogenic hormone may stimulate a pancreas which is in a condition of depressed function (low initial value) and inhibit the same organ in state of hyperactivity or high initial value; it may have no effect at all on a pancreas in a certain medium stage of activity. This positive or negative effect may be raised to a point where it produces corresponding anatomical changes and thus creates virtually a new organ obeying different rules.

A good example of this seems to us the fact that Young's diabetogenic extract which is capable of producing permanent diabetes and degenerative changes in the islets of a dog has the opposite (insulo-stimulating) effect in rats. (166, 48). The rat is notoriously not very sensitive to insulin as well as to pancreatic lesion. In contrast to this the pancreatropic (insulo-stimulating) extract is ineffective in the rat (243). One could express the same in terms of the "law of initial values" in the following way: the islet organ of the rat is probably as a rule in a state of low activity (low initial value). Such an organ is easy to stimulate, difficult to depress. Therefore what for the dog constitutes a small insulo-depressing dosis will be ineffective altogether in the rat. What for the dog is a large inhibiting dosis is a small stimulating dosis for the rat. Inhibiting doses for the rat would have to

be so large that they could not be used. All this applies, of course, to the rat pancreas in a certain medium state of function. The rabbit seems to hold in this respect a middle position between the dog and the rat (48).

Concerning the probable point of attack (effector organ) of this hormone or hormones of the carbohydrate metabolism, we are in accord with the majority of authors if we attribute the main role to the islets of Langerhans despite the fact that the diabetogenic hormone aggravates even the diabetes of the pancreatized animal. To explain the latter phenomenon as well as various observations concerning a direct effect on the liver glycogen we have to assume an additional direct action on the liver (103).

THE TROPHIC INFLUENCE OF THE ANTERIOR PITUITARY ON THE PANCREAS IN ANIMALS

For the purposes of this article it seemed particularly important to review more carefully the available data concerning the influence of pituitary on the histology and secretion of the islets of Langerhans.

A. Extirpation of the hypophysis. It has been for many years a tacit assumption that the removal of the anterior pituitary results in a kind of general microsplachnia, an atrophy of all inner organs while aeromegaly has the opposite effect (maerosplachnia). However, in older papers on the subject we mostly look in vain for microscopical examinations of the pancreas (221, 227). Even today these data are scarce. And yet already B. Aselmer who was the first to perform successful hypophysectomies found the pancreas to be *normal*. Meythaler (172) found in dogs a few months after the operation the islands about 15-20 per cent *larger* in size and number and a new kind of big nuclei, probably a sign of hyperactivity. Koster (123, 56) found in dogs all glands atrophic except the adrenals and thymus (which was rather large); the pancreas was atrophic but the *islets were normal*. P. E. Smith (204) found that hypophysectomy has about the same effect in all common laboratory animals and also in monkey and man: involution of adrenal cortex, gonads, thyroid, thymus; the pancreas was *not affected*. Houssay (104) found *no pancreas lesion* in dogs. Mahoney (155) who produced in puppies severe hypoglycemia by hypophysectomy found all endocrine glands hypoplastic with the exception of pancreas which was *swollen* and congested but showed no distinct histological changes; the diencephalon was examined and found to be normal. Crowe and co-workers (37) find the pancreas either *normal* or (in one case) *large islands* with peculiar arrangement of cells. Klug (119) found in two adult dogs one and a half and two years after hypophysectomy all glands including pancreas *normal*; only the gonads were atrophic in one of the dogs. Smith (quoted by Rivoire 194) found in the frog pancreas and parathyroid atrophic along with other glands but *never as much* as thyroid, gonads or adrenals. Leblond (135) comes to a similar conclusion. Marks and Young, Adams (207, 160) found in rats 30-60 days after hypophysectomy the

moss of islands doubled and returning to normal after injections of anterior pituitary extract; the same was found in salamanders; here the *number of islets was growing* while the total weight of the pancreas was decreasing (probably due to atrophy of other tissues); here again pituitary extracts decreased the number of islets while increasing the total weight. Anselmino and Hoffmann (6) found three and a half days after the operation the pancreas unchanged; they did observe a number of giant islets but found them in controls just as well. Griffith and Young (85) found in wistar rats with extirpated hypophysis another strange phenomenon: the total weight of the pancreas decreased (comparatively more than the body weight) but nevertheless the *insulin content was normal or even larger* than in controls; after injections of crude antero-pituitary extracts this insulin content became normal or subnormal. Haist (91) found the insulin content of the pancreas in hypophysectomized rats and dogs normal on normal diet and no effect of pituitary extracts. Krichevsky (130) saw in hypophysectomized rats the ratio of island tissue in proportion to body weight *increased* by about 65 per cent; on application of pituitary extracts it dropped to 34 per cent plus; the total body weight remained unchanged: Similar results in newts were reported by Adams and Ward (2). The interesting observations by Griffiths (68, 84) point toward a possible explanation of certain controversial results; if in growing Wistar rats hypophysectomy has been performed at a body weight of 80 gm. growth stops, pancreas becomes atrophic but the *insulin content increases*; if, however, the operation is performed at a body weight of 100 gm. we have also stopping of growth, reduction in body weight, atrophy of the pancreas, and diminished insulin content and which is not out of proportion to the decrease in body weight; in the latter case pituitary extracts increase both growth and insulin content. Van Dyke (221) summarizes his own and other experiences in this field as follows: atrophy of adrenal cortex in all amphibians and mammals; thymus shows atrophy or hypertrophy in rats; in dogs atrophy of gonads, adrenals, thyroid, degeneration of parathyroid in two-thirds of all cases, controversial findings in the thymus; pineal normal; regression of corpus luteum in mice and guinea pigs; atrophy of the liver in rabbits, in cats atrophy of liver, gonads, thyroid and adrenal cortex; in rats also atrophy of the adrenals; the pancreas is not mentioned among the atrophic organs.

In addition to this there is also some evidence of increased insulin content in the blood of hypophysectomized animals (221, 36, 194).

The conclusion we have to draw from these experiments and which will be confirmed later by cases of human pathology is this: *the anterior pituitary does not exert the same trophic and secretory influence on the islets of Langerhans as it does on most other organs. Hypophysectomy leaves the organ of insulin production unaffected or causes a hyperfunction or even hyperplasia of the islets.*

It would be interesting to speculate why it is so.

Has it something to do with the fact that the pancreas has a predominantly parasympathetic, thyroid, adrenals, gonads predominantly sympathetic innervation? Or with the fact that the islet organ is endowed with a great al., gonads predominantly sympathetic innervation? Or with the fact that the islet organ is endowed with a great and excretory tissue in the pancreas? A satisfactory answer to these questions cannot be given at present.

B. *Effect of antero-pituitary extracts on the pancreas.* If our conclusions are correct we would expect that injections of such extracts would have an effect opposite to that of hypophysectomy i. e. atrophy of the islet tissue. This is actually so. Of course, in case of extracts some contradictions are to be anticipated (217).

Young and many others after him have found that in dogs large doses of "diabetogenic extract" cause early changes in the beta-cells of the islets in form of degranulation; after about seven days this degranulation is almost complete and mitotic figures appear not only in the islets but also in the acini and ducts, this is followed by hydropic degeneration of beta-cells and vacuolation of intralobular ducts; where permanent diabetes has been established they have found extensive degeneration of beta-cells with hyalinization and but few normal beta-cells left (195, 92). In cases of functional recovery we find parallel anatomical recovery. The insulin content decreases rapidly after a few daily injections and recovers only if the injections had not been continued too long (16, 15). However, while the insulin content decreases by as much as 88 per cent the total weight of the pancreas may at the same time increase by thirty per cent (160).

Young's findings were confirmed by Campbell (24) and others. Similar though more irregular results were obtained in cats and other animals (153, 48) and with other extracts (17). In rats in which diabetogenic extracts produce paradoxical i. e. pancreatropic effects (160) we see also the insulin content doubling while the weight of the pancreas remains unchanged despite an increase in body weight by fifty per cent. It is noteworthy that these effects decrease with the continuation of the treatment (5). Even where definite acromegalic changes in the bones have developed the pancreas does not participate in this growth (151). Like in human pathology the individual variations are considerable.

But the main result of those experiments must not become obscured despite all objections: by injections of "diabetogenic hormone" under certain conditions we are able to produce temporary or permanent diabetes with corresponding degenerative findings in the pancreatic islets of certain species of animals. In this way we have here the expected opposite of hypophysectomy.

PANCREO-PITUITARY RELATIONS IN HUMAN

PATHOLOGY AND THE METABOLISM OF CARBOHYDRATES

In the field of human pathology and pathophysiology we expect to find analogous conditions. Main attention

is directed toward the clearcut picture of destruction of the anterior lobe of the hypophysis known in the clinic as Simmond's or pituitary cachexia in the adult and as pituitary dwarfism in the individual affected in his childhood. In place of experimental hyperpituitarism produced by injections of extracts we have in human pathology a clearcut picture of spontaneous hyperfunction of the anterior lobe in acromegaly which compensates for our limitations in the dangerous experiment of producing diabetes in man. We shall again review separately the functional findings as far as the metabolism of carbohydrates is concerned and the anatomical findings in the pancreas in pituitary diseases.

A. HYPOPITUITARISM

In hypopituitarism in general we find in analogy with the animal a tendency toward hypoglycemia. The material is comparatively small. After all our knowledge of pituitary cachexia is only about three decades old and little attention has been paid until recently to the sugar metabolism in this disease. Blood sugar was mostly found low or normal (117a). In a recent review of the literature Lisser and Escanilla (143) give the following data on 106 cases of pituitary cachexia; 83 cases without autoptic verification had an average value of 80 (low normal) while 23 cases with autopsy had an average value 66 mgm. per cent; the latter group comprises, of course, the older and more severe cases, many of whom probably were killed by hypoglycemia. We know of only one case (191) in which the spinal fluid sugar was determined and found very low.

Hypersensitivity to insulin is emphasized by a number of authors (117a, 111, 210, 147, 173, 140, 65). Some stress the delay or absence of secondary rise of blood sugar after insulin (117a, 190, 64, 65). We encounter examples of special sensitivity like the case described by Rau (190) in which the blood sugar dropped after only ten units of insulin to forty mgm. per cent in 75 minutes and remained on that level for 24 hours despite intake of sugar. Lichtwitz (140) mentions that as little as two units may cause severe symptoms of hypoglycemia. In one of our cases, a combination of tuberculosis of the anterior lobe with insuloma of the pancreas (223), one unit of insulin given intradermally seemed to change the day blood sugar curve on a fixed diet from 117-117-86-156-131 to 76-98-88-67-70 mgm. per cent. We wish to emphasize here for practical purposes that an injection of insulin in pituitary cachexia may easily prove a highly dangerous procedure. This is necessary to emphasize in view of a few reports of cases, not autoptically verified, in which clinical improvement was achieved by insulin therapy (97, 210). This oversensitiveness although characteristic in hypopituitarism is not specific; it can be found, e. g. in Addison's disease and in certain cases of hyperinsulinism.

Another characteristic feature of pituitary disturbance in the carbohydrate metabolism, *sensitivity to starvation*, has been noticed several times in human

pathology although not sufficiently studied (117a, 65). In one case the disease became manifest after a reducing diet was instituted (129). We think such cases may prove to be more frequent especially among those in which the differential diagnosis between pituitary cachexia and anorexia nervosa is difficult to make.

From France, starving under the sadistic Nazi regime in World War II comes a series of reports about cases of starvation (mostly with edema) with severe hypoglycemia, often not responding to dextrose but responding to protein supply. In those cases the anterior pituitary was found destroyed and the question arises whether starvation produced the destruction of the pituitary or cases with lesions of the anterior pituitary responded so strongly to starvation (137, 76).

Some authors think that a drop in blood sugar after physical work is characteristic (117a) but it certainly is not specific since it also occurs in Addison's disease.

Personally we were unable to find a blood sugar tolerance curve specific for pituitary diseases (230). Most authors find the rise after ingestion of glucose below normal (117a) but some find it above normal (147) and the ensuing hypoglycemia deeper than normal. Other authors find flat curves, etc. (140, 129, 117a, 210, 191, 139, 147, 167, 190, 140, 136). In general we agree with Lissner and Escamilla (143) who speak of a "tendency to hypoglycemic levels;" this tendency in various forms they found in 42 per cent of 19 verified and in 19 per cent of 53 not verified cases. In rare cases we find hypoglycemia accompanied by glycosuria (210) but as a rule we can find an increased tolerance (147, 17, 51, 210, 53). In contrast to the insulin-sensitivity we find also an increased adrenalin blood sugar curve (117a, 147, 190).

In one case who died with hypoglycemia the liver glycogen was determined and found normal (117a).

The occurrence of clinical syndromes of hypoglycemia is much more frequent than the literature would indicate. This author (229) was the first to insist that "pituitary spontaneous hypoglycemia" is a clinical syndrome sui generis; Goldzieher (75) and others described interesting examples of that syndrome. The reason why hypoglycemic symptoms have been rarely mentioned in the literature is the fact that until recently the physicians were not familiar with them. Although such symptoms can be easily recognized from the description of the cases only some authors diagnose them as such (229, 117a, 53, 40a, 210, 140). The most frequent symptoms of hypoglycemia in those cases were; coma, stupor, drowsiness, fatigue, confusion, epileptiform seizures, disturbances of gait, speech, handwriting, choreiform movements, tremor, rigidity of muscles, fainting spells, depression, etc. Since mental symptoms are most frequent in hypoglycemia (231) it should be noted that a survey of 200 cases of Simmond's disease showed mental symptoms present in 50 per cent of the cases (239); most cases were not tumors.

Recent figures by Sheehan (205) corroborate these statements. Sheehan compiled 32 cases of verified necrosis

of the anterior lobe. In 50 per cent the blood sugar was 60 to 70 mgm. per cent, in the rest of the cases higher. The blood sugar tolerance curve (followed for three hours only) was usually prolonged, sensitivity to insulin increased. In a number of cases deep hypoglycemia was found in the terminal coma and two out of five such cases were saved by glucose injections. This coma was mostly provoked by insufficient food, anorexia or vomiting. Severe emaciation was uncommon, seven patients were normal or obese. This author (229) has emphasized the occurrence of "pituitary cachexia without cachexia" in cases with relative hyperinsulinism. The frequent mental symptoms described by Sheehan remind us strongly of hypoglycemia: asthenia, dullness, listlessness, indifference, deconcentration, loss of initiative and spontaneous interest, forgetfulness, distrust of doctors and in more severe cases sluggishness of mental processes, slow, slurred and monotonous speech, somnolence, cataplexy, psychotic syndromes (see Wilder 227a).

Experience shows that all these phenomena can be reversed or influenced by specific hormones of the anterior pituitary. However, the results are far from uniform. We have cases in which the fasting blood sugar rose from 0 to 80 mgm. per cent under the influence of transplantation of a pituitary gland (163). In other cases the blood sugar curve improved under influence of anterior pituitary extracts (87). Like this author Steinitz and Thau (210) saw no immediate effect on the blood sugar from crude extracts (230) but continued medication raises it.

Thus in our case (232) of destruction of the anterior pituitary combined with insuloma of the pancreas the crude extract praephyson injected at bedtime delayed the regular hypoglycemia in the morning by several hours while prolactin and other endocrine preparations did not have this effect. Young made similar observations on dogs. Certainly we would not expect this effect to be specific and the sugar metabolism as other symptoms of Simmond's disease may be influenced e. g. also by adreno-cortical hormone (129) despite the fact that the main diabetogenic effect of the anterior pituitary hormone has nothing to do with the adrenals.

In our aforementioned case cortigen given in the morning had no distinct effect on the day blood sugar curve; the latter was 55-119-67-91 with and 57-153-75-66 without cortigen. Cortigen had some effect on the alimentary hyperglycemia following 100 gm. dextrose; 57-121 (30 min.) 167-157-96-64 without and 53-49-44-128-74-92 mgm. per cent with cortigen; the immediate effect was depressing like that of antero-pituitary extracts.

In pituitary dwarfism we do not necessarily expect metabolic disturbances since the condition occurs in childhood and the developing organism has time to adapt itself to the resulting endocrine deficiency. Nevertheless we find in some cases evidence of disturbed sugar metabolism like low fasting levels (147, 164), increased tolerance for carbohydrates (147), deep secondary hypoglycemia after a high peak in the blood sugar tolerance test (147). Clinical symptoms of hypoglycemia are hardly ever mentioned. The adrenalin blood sugar curve (147) is high (like in Simmond's disease) or absent (237). The sensitivity to insulin is increased (147). It is interesting that similar conditions have been found in dwarf mice with

under-developed anterior pituitary lobe (176). We are not too surprised to find an infrequent case of pituitary dwarfism combined with diabetes (47, 189). This seems to occur more often than combination of pituitary cachexia with diabetes (127). Possibly here too observations on dwarf mice contain a clue to this phenomenon: the pancreas in these animals shows normal weight but atrophies with high age (116, 16).

A number of less clearcut pictures mostly lacking autoptic verification have been described in the literature as hypopituitarism. Here again we find the same trend toward hypoglycemia. We may mention the "pituitary thinness" (118) cases of subtotal hypophysectomy in man (209), the more or less vague clinical syndromes described in the literature as "pituitary insufficiency" (202, 139, 30, 81, 49, 38, 158, 83, 182, 42, 44a, 71, 242).

B. HYPERPITUITARISM

In hyperpituitarism we expect and find a behavior of the sugar metabolism which is the exact opposite of hypopituitarism. Since the eosinophilic cells of the anterior lobe have been linked in first place to growth as well as sugar metabolism we have to discuss first the eosinophilic adenoma and its clinical correlate *acromegaly*. The frequency of diabetes in acromegaly has been discovered as early as 1898 by Pierre Marie. The frequency of this diabetes is given by various authors as low as 10 and as high as 40 per cent (149, 32, 111, 114, 20, 53, 44a). There exists a considerable discussion in the literature whether and how this acromegaly-diabetes differs from ordinary pancreas diabetes. Joslin (111) and others find no real differences except for striking variations in intensity and spontaneous cures (20). Joslin goes as far as to say: "Practically the only temporary or permanent cures of diabetes recorded are those cases in which a pituitary factor has been present." The variations in intensity of the diabetes are sometimes linked to similar variations in other symptoms of acromegaly (waves of acromegalism). A characteristic example of changes in the diabetic condition is a case of acromegaly described by Lichtwitz (141) which first showed a blood sugar curve characterized by a moderate rise and sharp drop, then developed a diabetes resistant to insulin with severe coma and became normal after ten days. The following differences have received attention in the literature but did not remain uncontested; 1. lesser response to insulin (11, 44a, 59, 52a, 32); 2. more difficult management with diet and insulin (11, 185); 3. lack of insulin response when insulin is combined with pituitrin (111, 226); 4. relative independence from diet (179, 20); 5. polyuria more outspoken than in pancreas-diabetes (32); 6. the clinical features of diabetes like thirst, polyphagia, furunculosis, chorioretinitis, etc. may be absent (32); however, we undoubtedly find in many cases all forms and symptoms of diabetes mild, moderate and fatal like e. g. the famous case by Lancereau which excreted up to 1500 gm. sugar daily (199); 7. some authors maintain that the tendency to coma and acidosis is less than in diabetes mellitus; 8. lack of dis-

turbances of the N-metabolism except for increased excretion of endogenous purin derivatives; 9. the basal metabolism is mostly moderately increased in acromegaly (40, 44) but Cushing and Davidoff found also cases (6 out of 49) with lowered basal metabolic rate (40). Besides real diabetes we find in acromegaly quite often a purely alimentary glycosuria (20, 32). Davidoff, e. g. in his classical studies (44a, 43) has found glycosuria present in one fourth, outspoken diabetes in one eighth of the total cases examined. Other authors, however, have found glycosuria in only one tenth of their cases (185).

The combination of acromegalic and diabetic symptoms sometimes found in pregnancy has been attributed to hyperpituitarism (29).

Some authors state that diabetes usually appears comparatively late in the course of acromegaly (53). In Coggeshall and Root's material of 29 cases, e. g., symptoms of acromegaly preceded diabetes by an average of 9.2 years (29). Only Sainton and Roi (199) find diabetes to be an initial rather than terminal symptom in acromegaly. In this they obviously are only partly right: diabetes is not a terminal symptom of acromegaly; but neither is it an initial symptom; it is rather so that diabetes is likely to develop after acromegaly has existed for some time and on the other hand it is likely to disappear in the further course of disease when the eosinophilic tumor is damaged by intracellular pressure — a phenomenon comparable to hypophysectomy in a pancreatomized dog (Houssay-effect). This rule, of course, will have a number of exceptions in individual cases. It seems that occurrence and severity of diabetes bears no relation to the size of pituitary adenoma (44a). After surgical removal of the adenoma the basal metabolic rate drops to normal (40), for instance from an average of plus 14 to an average of minus 7 (44) and the coexistent diabetes may disappear (44a); X-ray irradiation of the tumor may have the same effect (11, 49).

This is not the place to discuss the interesting details of the acromegalic sugar metabolism in general. Where there is no outspoken diabetes we find in many cases diabetic or hyperglycemic tendencies in the fasting blood sugar, sugar tolerance, etc. Increased tolerance is mostly found in cases of long standing (52a, 38) or following operation or X-ray therapy.

In contrast to pituitary cachexia the sensitivity to insulin in acromegaly without diabetes is mostly diminished (32, 152, 11). Fernbach (57) found the insulin sensitivity more diminished in other brain tumors (including other pituitary tumors) than in acromegaly; he found the subjective symptoms of hypoglycemia less marked in acromegaly than in other tumors.

The lack of uniformity in the disturbances of sugar metabolism in acromegaly is not surprising if we keep in mind that we are dealing here with tumors. Mild and severe, old and new, slowly and rapidly progressing cases are expected to show differences in this respect. Two of those differences deserve more at-

tention: 1. that between old and recent cases and 2. that between obese and non-obese cases. Those two groups overlap to a great extent since obesity, if at all, usually appears in the later stages of the disease. The best explanation is that an old adenoma goes into a stage of hypofunction due to exhaustion, degeneration or pressure. Pressure on or invasion of the neighboring hypothalamic centers may play a role (53). Where this is not the case we would have to think of compensatory mechanisms of other endocrine glands and, last not least, of a late increase in sugar tolerance and relative hyperinsulinism leading to obesity (179, 32, 53, 93). A typical case in question may be quoted (49): acromegaly, blood sugar curve (1.75 gm. glucose per kgm. body weight) in three hours is 162-305-294 mgm. per cent; one year later after X-ray therapy the curve drops to 93-121-107 mgm. per cent under increase in body weight by 30 kgm.

We cannot confirm or deny from personal experience the statement made by John (114) that in cases of pituitary tumors with diabetes (and without acromegaly) there were in the history mostly acromegalic features preceding the diabetes. These cases are not frequent (32). Cases with increased instead of decreased sugar tolerance often bear marks of involvement of hypothalamic centers or of pituitary hypofunction besides obesity: eunuchoidism (1), arrested or partial acromegaly (223, 229).

We do not possess data on *gigantism* corresponding to those in pituitary dwarfism. Possibly the frequent giant infants of diabetic mothers belong here.

C. OTHER PITUITARY SYNDROMES

The endocrine situation in pituitary disease other than atrophy and hypertrophy are certainly too complicated to draw theoretical conclusions. However, it may be of some interest to see what data on sugar metabolism they yield.

1. *Basophilic adenoma* shows in its sugar metabolism a similarity with the basophilic and eosinophilic adenoma (35, 222, 8, 173, 111, 100, 86).

2. *The chromophobic adenoma* behaves as far as sugar metabolism is concerned like pituitary cachexia (44a, 162, 60, 236, 206, 35).

3. *Other pituitary tumors*, like Rathke's pouch tumor, etc. behave in respect to sugar metabolism more often like hypo- than hyperpituitarism (183, 185, 56, 32, 57, 180, 167).

4. *Various clinical syndromes* attributed to the hypophysis are e. g. the "*pituitary diabetes*" the isolation of which has been attempted without much success as far back as 1884 (32, 199); at that time it was attributed to the posterior pituitary. Modern studies may clarify this problem in the future (86, 82). *Froehlich's dystrophia adiposo-genitalis* in which the sugar metabolism may be normal or show all kinds of deviation (117, 186, 109, 53, 203, 53a, 74, 139, 78, 179, 52a, 214, 156, 35, 180, 167, 22, 24a, 201, 131); *pituitary obesity* without genital atrophy, a debatable syndrome and often connected with other symptoms like narcolepsy, etc. shows hypoglycemic tendencies (8, 70).

THE TROPHIC INFLUENCE OF THE ANTERIOR PITUITARY ON THE PANCREAS IN HUMAN PATHOLOGY

A. SIMMOND'S DISEASE

In a previous chapter we have surveyed the rather scant data on the relation of Simmond's disease to the metabolism of carbohydrates in the clinical picture. In this chapter the material to be reviewed is still smaller and it concerns the pathology of the disease with special reference to the islet organ of the pancreas and — whenever possible — to the sugar metabolism.

We shall quote in first place a survey by Sheehan of 32 cases of verified necrosis of the anterior lobe of the hypophysis (205). The blood sugar was low (60-70 mgm. per cent) in 50 per cent of the cases. The pathological findings in this series showed the thyroid, adrenal cortex, parathyroids mostly atrophic, the adrenal medulla mostly normal, the pineal (two cases) rather large; the islets of the pancreas were *mostly normal* (small in three cases). Two cases had hypothalamic lesions, in two others the hypothalamus was normal.

In our own compilation of 26 cases with autopsy three were men; one had the anterior lobe destroyed by gummata, two by tuberculosis, the rest were cases of fibrosis probably of vascular origin. The majority had clinical symptoms which could be the result of hypoglycemia although they were rarely diagnosed as such; various seizures, personality changes, etc. 15 out of 30 cases surveyed had blood sugar tests fasting or in the attack with occasional levels below 50 mgm. per cent, in 10 even as low as 17-35 mgm. per cent. The latter cases did not differ either clinically or anatomically from the rest of the cases. We were unable to find any direct correlation between blood sugar and hypoglycemic symptoms on one hand and size of the pancreas on the other. Neither was in this series any correlation evidenced with sex, age or duration of the disease.

The survey of pathological findings seem important. The size of the pancreas was normal in 8, slightly above normal in one, diminished in 14, not given in two. The cases with small pancreas showed a reduction in size compared with the norm by 10-78 per cent, the mean size in ten cases being 56 per cent of the norm. The microscopical examination showed normal findings in the cases with normal and in the one with slightly increased size. Important were the findings in the cases with small pancreas; in every single case the atrophy involved the acini exclusively while the *islet tissue was either normal in size or increased*. The connective tissue was increased in amount in some of the cases.

Our attempt to correlate these findings with those in other endocrine glands gave the following results:

1. the *thyroid* in all cases showed more or less marked atrophy; the loss in weight was more marked than in the pancreas in 5 out of 9 cases and less marked in four; microscopically though the atrophy of the parenchyma was in all cases more pronounced than it was in the pancreas;

2. the *adrenals* were with one exception reduced in size; where figures were available this reduction was considerable (14-37 per cent of the normal size) and mostly more marked than that of the pancreas; yet this atrophy involved the cortex exclusively;

3. the *gonads* were atrophic in all cases; the atrophy was always very outspoken; the data available do not allow to correlate it with the size of pancreas;

4. the *parathyroids* in the few cases available were absent, atrophic or degenerated;

5. the *pineal* was measured or weighed in three cases; the data are contradictory.

We have also tried to correlate the data on the pancreas with those of other organs:

1. the *liver* shows a decrease in weight in 11 out of 12 cases examined; this reduction is partly more partly less marked than that of the total body weight but with one exception it was more marked than that of the pancreas; the one case with normal weight of the liver had no cachexia or microsplachnia except for myocard, thyroid and adrenals; the pancreas was not atrophic; the one case with the pancreas comparatively more atrophic than the liver (pancreas 24, liver 46 per cent of the norm) was a 69 year old individual with marked cachexia and microsplachnia; the islets were normal in number; these two cases have been ill for over 30 years;

2. the *heart* (myocard) was reduced in size in all cases, either more or less than the total body weight but with one exception always more than the pancreas;

3. the *kidneys* were mostly but not always reduced in size; where this was the case the atrophy was more outspoken than that of the pancreas with the exception of the 69 year old patient mentioned above.

The conclusions we may draw from these data are the following: *the general statement that destruction of the anterior pituitary lobe in man is followed by cachexia and microsplachnia has to be qualified. From the endocrine glands the gonads, the thyroid, and the adrenal cortex are particularly affected by the resulting atrophy while the pancreas either does not take part in this process at all or to a lesser degree than the other organs. But even where the pancreas shows some atrophy it is the acinar tissue which atrophies while the islets remain unaffected. What is more, in a number of cases there is evidence of an absolute increase in the amount of islet tissue.* Thus three glands which elevate the blood sugar are partly eliminated; the anterior pituitary, thyroid and adrenal cortex while their antagonist in this respect, the islet organ, remains unaffected or even shows hyperplasia. To this we may add the partial elimination of the liver and the atrophy of the acinar tissue of the pancreas; the latter exerts an antagonistic effect on the islet organ. It is possible that the atrophy of the gonads plays also some minor role in this picture. Under these circumstances we should not be surprised to find hypoglycemia in the wake of destruction of the anterior pituitary lobe. It is rather the case of Simmond's disease with normal sugar metabo-

lism which calls for special study and explanation. At any rate, the findings in human pathology parallel those in hypophysectomized animals.

Cases used in this survey: 165 and 122, 95, 239, 14, 212, 54, 72, 96, 42, 196a, 55, 108, 240, 174, 138, (2 cases), 69, (2 cases), 187, 184, 218, 215, 26, 79, 110, (2 cases), 168, 52, 142, 3, 207. Only two of them were also used by Sheehan in his survey. Another series of cases dealing with adenomata of the islets in destructive lesions of the anterior pituitary is discussed later in this paper.

B. ACROMEGALY

We have discussed before why we cannot expect acromegaly to be a cleareut exact counterpart of hypopituitarism. And yet in the case of the carbohydrate metabolism and the endocrine interrelationships it is more so than we would expect. If our conclusion concerning pituitary cachexia were correct the exact opposite would be: pancreas normal or large in size with hypertrophy of the acini and the islets normal or atrophic; hypertrophy of the thyroid, adrenal cortex, gonads and perhaps the parathyroid; hypertrophy of liver, heart and often kidneys. We shall see soon how very close the real facts come to these expectations.

In the older literature which rarely mentions the pancreas and almost never the microscopic examination of the islets we find mostly sweeping statements concerning the splanchnomegaly of all inner organs including the endocrine glands. With the improvement in the pathological examinations these statements become more and more qualified and restricted. We hear for instance that the pancreas is "not often" enlarged (149), the findings in other endocrine glands vary, etc. Sehulte found the pancreas abnormal in only four out of 49 cases of acromegaly. Pineles found pancreas lesions in only three out of 17 cases of aeromegaly-diabetes (32). More recently Colwell (32) found among 15 cases seven with atrophic, four with hypertrophic and three with other changes in the pancreas; two of these cases had no diabetes. But some authors still find the pancreas enlarged in the majority of cases (5, 29). Cushing and Davidoff (41) have found so many discrepancies in their findings that they speak of "dysproportionate splanchnomegaly" and tendency to adenomatous hyperplasia as characteristic of acromegaly. This term is certainly justified in view of the fact that other glands too show great variety in their findings (213, 53).

In our own survey of the literature the emphasis was not only on the weight but also on the histological findings in the pancreas, the most neglected among the endocrine glands. This is necessary, if for no other reason, than for the well known fact that the connective tissue in various organs shows a special hyperplastic trend in acromegaly and accounts for much of the increase in weight. The size of the pancreas was given in 24 out of 32 cases; in 17 cases a microscopic examination was done. The size (weight) was above normal in 16, normal in six, subnormal in two. This comes very close to an exact opposite of the findings in pituitary cachexia which showed the

pancreas above normal in one, normal in eight and subnormal in 14 cases. Like in pituitary cachexia we find in acromegaly that the mere size of the organ gives us a false picture of the condition of the functioning endocrine tissue. In pituitary cachexia the islets were mostly preserved or hypertrophic in a small pancreas. Here we find the opposite: in one case in which the size was reduced to 59 per cent of the norm we find acini and interstitial tissue normal, islets diminished in size with hydropic degeneration; in 18 cases in which the weight was increased or not given there was hyperplasia of the islets (nodular in one) in only two cases; in one case the first report was normal, a later one speaks of possible hyperplasia; in one case we have a combination of adenomatous hyperplasia with degenerated islets; in one case normal islets, and in the remaining 13 cases various degrees of regressive changes in the islets: decrease in size and number, sclerosis, hydropic degeneration, and some peculiar findings like: adhesive peritonitis or hemorrhages. The findings in the acini show no uniformity; we find normal, hypertrophic as well as markedly atrophic acini. One of the most constant features is the increase in the amount of connective tissue which is chiefly responsible for the increase in weight. J. E. Kraus (128) to whom we owe important pathological studies in this field says directly that the pancreas as a rule is enlarged because of proliferated interstitial tissue; he found hydropic degeneration and atrophy of islets even in some cases with normal carbohydrate metabolism.

There are no sufficient figures in our series to correlate the weight of the pancreas with that of other organs or the total body weight as we did in Simmond's disease. The adrenals are often enlarged; this hyperplasia, again the exact opposite of Simmond's disease, concerns almost exclusively the cortex and often nodular or adenomatous in type. The thyroid is mostly but not always enlarged and shows various forms of goiter with much connective tissue; the parathyroids show hypertrophy of the acidophilic cells with tendency to formation of adenomata; the thymus is often but not always enlarged; the gonads are mostly atrophic or degenerated. Thus with the exception of the gonads which show atrophy in both diseases we see in acromegaly the opposite of pituitary cachexia. We can speak not only with Cushing and Davidoff (41) of disproportionate splanchnomegaly in acromegaly but also of disproportionate splanchnomicria in Simmond's disease. It would be also correct to speak of dystrophy in both cases and since this disproportion applies not only to organs but also to tissues (islets-acini, adrenal cortex and medulla, connective tissue-parenchyma) we suggest the term *histodystrophy with predominantly hyperplastic form in acromegaly and predominantly hypoplastic in pituitary cachexia*. Since this is not only a matter of new names but also of a new concept it might prove important in the future. For instance, the concept of trophic tendencies acting on certain tissues rather than on certain organs would center our interest on biochemical factors of growth rather than on the nervous system.

As far as sugar metabolism in this series is concerned we must keep in mind that even in ordinary pancreas diabetes there is no quantitative relationship evident between the degree of diabetes and degree of pancreas lesion. We know, e. g., that Warren (241) found the pancreas normal in no less than 30 per cent of cases of diabetes mellitus. This keeps us from being too disappointed with our findings in acromegaly: out of 12 cases in which the weight of the pancreas was given we find in two cases normal weight and one of them had diabetes; one case with diminished weight had no diabetes; and out of nine cases with increased weight six had diabetes. The situation is not clearer in the 14 cases in which we have a microscopical examination of the pancreas: out of 10 cases with atrophic islets seven had diabetes; but one case with normal and two with hyperplastic islands also had diabetes and one case with mixed hypo- and hyperplasia of the islets had no diabetes.

Cases used in this survey were: 2, 4, 21, 44a, 53, 61, 94, 127, 121, 125, 177, 225, 213, 200, 29, 120, 89, 126, 127, 177.

We must add that many of the microscopical studies even in this series were far from perfect: the functional condition of the islets as expressed in the staining of the beta granules was considered but in a few of them; the usual count of the number of islets in a field was not correlated with the increase in connective tissue between them, etc.

We can draw certain final conclusions from those findings in both acromegaly and pituitary cachexia. In 1930 we formulated a hypothesis (229) to the effect that we may expect a disturbance of equilibrium in form of *relative* hyperinsulinism and hypoglycemia in those cases of Simmond's disease in which the pancreas fails to atrophy; and that correspondingly we shall see diabetes in those cases of acromegaly in which the islet organ does not keep in step with the other organs as far as hyperplasia is concerned. At that time we did not consider seriously enough the additional possibility of *actual* instead of *relative* hyperinsulinism due to hyperplasia in hypopituitarism as well as actual atrophy and hypoinsulinism in acromegaly. Today, although this theory is not true if considered case by case, we can say in general this: in pituitary cachexia we find very often clinical hypoglycemia and anatomically either normal or hyperplastic islets of Langerhans; *vice versa* in acromegaly we find very often hyperglycemia or diabetes and anatomically atrophic or degenerated islets. Case by case there is no direct parallelism between the clinical and anatomical findings.

C. COMBINED PANCREO-PITUITARY DISEASES.

Houssay's experiments on totally or partly pancreatized and hypophysectomized dogs operate with combined pancreo-pituitary lesions. Human pathology offers examples of such combined lesions which pose interesting problems. We have collected a series of eleven cases from the literature including one from our own records which present the opposite of the Houssay-dog. Ten of them had clinical and laboratory find-

ings of spontaneous hypoglycemia, one had no blood sugar tests but was clinically suspect (dizzy spells). All these cases had adenomata of the islets of Langerhans; three of them had even several such adenomata and four of them had hyperplasia of the islets in addition to adenoma. What is interesting in those cases of insuloma are the findings in the pituitary which we want to quote case by case:

Tehrüggen's case (216) had two microscopic chromophobic cell adenomata; Heupke and Obert's case (98) had a malignant probably basophilic adenoma the size of a chestnut with complete destruction of acidophilic cells; Rienhof and Lewis report tiny adenomata and an increased number of basophilic cells (193); Malamud and Grosh (157) found a small basophilic adenoma and diffuse eosinophilic hyperplasia; Friedman and Blau, Reider and Bender (66, 18) had in both of their cases basophilic adenomata, two and four mm. in diameter respectively, adenomatous hyperplasia of the anterior and massive basophilic infiltration of the posterior lobe; Farquarson and Graham (55) had in their case two basophilic nodules, one and four mm. in diameter and one eosinophilic two mm. in diameter in addition to an increased number of both baso- and acidophilic cells and basophilic infiltration of the posterior lobe; Barnard's case (107) had only a slightly enlarged anterior lobe and large islands of squamous epithelium in the anterior part of the stalk; Lloyd's case (144) showed a huge chromophobic adenoma of the anterior lobe, our own case (229, 230, 232) had an advanced destruction of the anterior lobe by tuberculous tissue and basophilic infiltration of the posterior lobe. We have included here a case by Feinier and co-workers (56) who had no autopsy but presented clinically the picture of hypopituitarism with the X-ray findings of the sella turcica showing some atrophy; and a case by Shelburne and Mc Laughlin (208) who had an adenoma of the parathyroid (verified by operation) and a tumor of the pituitary (verified by X-ray).

Certainly the findings in the hypophysis of these cases of hypoglycemia are very varied and only in some of them have we the right to assume with certainty a loss of function of the acidophilic cells important for the sugar metabolism. We do not take into consideration microscopic adenomata which are perhaps within the range of normal variations (23). Only three out of the eleven cases may be considered strictly speaking the counterpart of the Houssay-dog. However, there are certain other findings in this series suggesting more than a mere coincidence: two of the series had also adenomata of the thyroid; two had small adenomata of the adrenal cortex (which by the way can be found in as much as 1.5% of the general autopsy material, (96); one had multiple small cysts of the ovaries; one had prostatic hypertrophy; three had tumorlike hyperplasia (two with adenoma) of the parathyroids; two had hyperplasia of the thymus; two had huge lipomata (one subpleural); one fibromyoma of the esophagus; one numerous papillomata of the skin; one a nondescript tumor of the uterus.

Incidentally four of the series had exact histopathological examination of the brain; only one had swelling and one minor changes in the hypothalamic nuclei; compression of the floor of the third ventricle was evident macroscopically in a fifth case. It seems that some hyperplastic trend manifests itself in these cases in various organs especially endocrine glands. This does not make us inclined to assume mere coincidence. The latter would be as far as pancreas and hypophysis is concerned a combination of very rare conditions: Lloyd found among 10,000 cases of autopsy only one case of insuloma; on the other hand among 19 cases of pituitary tumors he found in several instances "more than a suggestion" of hyperplasia of the islets (144).

If we do not assume a mere coincidence there are a few possibilities left. All the organs affected including the pituitary could be bearers of some common adenomatous tendency of unknown origin. Our case with a destructive lesion of the pituitary would not fit into this hypothesis. On the other hand the pituitary lesion could be in some way responsible for the adenomatous trends in other organs. This seems more probable if we consider the histodystrophy resulting in both destructive as well as as hyperplastic conditions in pituitary diseases. For a number of other reasons which we do not discuss here many authors have tried to establish a relation between the pituitary gland and the growth of various tumors. All these theories, however, are not yet based on a very solid foundation.

Even the best hypothesis in endocrinology will have to expect a number of exceptions because of processes of adaptation and compensation. We shall mention here a few interesting cases: a case of acromegaly with atypical eosinophilic adenoma of the pituitary, eosinophilic adenoma of the pancreas, "Hauptzellen"-tumor of the parathyroids, multiple adenomata of the adrenal cortex, colloid-cystic adenoma of the thyroid, benign pinealoma, thymo-lymphatic hyperplasia and multiple mesenteric lipomata (73). There are cases of a replica of the Houssay dog in man: destructive lesion of the pituitary and atrophy of the islets; one of these cases had a tuberculous lesion of the pituitary, chronic interstitial pancreatitis with atrophy of the islets, adenoma of the thyroid and small adenomata of the adrenal cortex; the diabetes was not abolished by the pituitary lesion (127). Other cases in which the diabetes persisted despite the pituitary lesion are quoted by Koehne (120). Chabanier and co-workers (27). Merle report partial improvement of diabetes after extirpation of normal hypophysis. In one case in which diabetes turned into fatal hypoglycemia there was necrosis of the anterior pituitary (patient suffered from tuberculosis), normal pancreas and changes in the ganglion cells of the hypothalamus (124). A more typical case of a "Houssay-man" is that of a cure of diabetes with the appearance of a progressive calcifying endosellar tumor (154). There are several cases of improvement of diabetes after X-ray therapy of the pituitary gland (134) but also many failures. Thus the few cases of "Houssay-man" on record did not help as yet in the clarification of the problem discussed above.

It is easy to answer the question whether the insuloma may not be responsible for the changes in the pituitary gland. We have many publications at our disposal to prove that the changes in the pituitary gland following oversupply of insulin are but minor

changes quite different from adenoma or necrosis as presented by our cases; controversial, minor or absent pathological findings are reported after insulin-intoxication or pancreatectomy (32, 194, 157, 221). This is true not only for animal but also for man (126, 219, 115, 220). Of course, we have also quite a number of cases of insuloma in man in which the pituitary gland was examined and found normal.

CONCLUSIONS

A survey of literature has been undertaken concerning the physiological as well as anatomical interrelationships between anterior pituitary gland and the islet organ of the pancreas in animal and man. The main goal was an attempt at orientation of the many controversial clinical and anatomical findings with full realization of the fact that due to the complexity of endocrine interrelationships we cannot expect rules covering every single case. We must be satisfied with the demonstration of principal trends.

It is considered as probable that the numerous hormones of the carbohydrate metabolism discovered in recent years and attributed to the anterior pituitary are but alterations of the growth hormone secreted by the acidophilic cells of the hypophysis. This applies especially to the diabetogenic hormone. It may be that the same is true for other hormones of the pituitary gland not directly concerned with the carbohydrate metabolism with the exception of the gonadotropic hormone which seems to be a separate hormone.

This survey shows that the anatomical as well as functional relationships between the anterior pituitary and the islet organ of the pancreas are not as simple as it has been assumed in the older literature: while, for most other organs and tissues the growth hormone is growth promoting (and this includes the acinar tissue of the pancreas) for the islet tissue its action is growth-inhibiting. What is true for the *trophic* effect is even more true for the *tropic* i. e. function-promoting effect of the growth hormone. Since the growth effect of the hypophysis is so different not only for different organs but even for different tissues within the same organ (acini-islets, adrenal cortex and medulla, connective tissue-parenchyma) it is suggested to speak of *histodystrophy* in pituitary diseases and of a *histodystrophic* function of the growth hormone. This histodystrophy is predominantly hyperplastic in hyper-, predominantly hypoplastic in hypopituitarism. The corresponding mixed pattern of stimulating-inhibiting effect on the various functions of the organs concerned could be called the *dystrophic* effect of the growth hormone.

As far as carbohydrate metabolism is concerned a deficiency in this specifically patterned dystrophic

and dystrophic function of the growth hormone will result mostly in hypoglycemia while an oversupply will result in hyperglycemia and diabetes. The reason for this imbalance in the metabolism of carbohydrates is a complex one. In case of deficiency we have; 1. relative hyperinsulinism caused by absence of the antagonistic antero-pituitary hormone; 2. absolute hyperinsulinism by hyperfunction or hyperplasia of the islets of Langerhans; 3. atrophy or hypofunction of other antagonists of insulin i. e. thyroid and adrenal medulla; 4. atrophy of the antagonistic acinar tissue of the pancreas; 5. atrophy of the liver which, if extensive, can lead to hypoglycemia. Acromegaly or injections of large doses of proper pituitary extracts will cause the exact reverse picture of this resulting in a diabetic tendency.

It seems that the imbalance in the sugar metabolism in pituitary diseases has a few characteristic though not specific features. Such are: hypersensitivity to insulin as well as (paradoxically) to adrenalin and to sugar-starvation in pituitary caectoxia, and corresponding hyposensitivity in acromegaly. A number of contradictory findings can be explained by the assumption of a separate effect of the anterior pituitary on the liver. Other controversial findings can be reconciled if we keep in mind the *opposite effect of small and large doses* of extracts and the *relativity of the concept "large" and "small"* depending on the momentary functional condition of the effector organ (law of initial values).

In practical application to the single case these rules are valid to a certain extent only not more than the rule that we find a pancreas lesion in every case of diabetes mellitus. It is to be hoped, however, that with the improvement of our experimental, microscopical and biochemical methods the field covered by these rules will become larger.

Finally special attention is called in this paper to the possibility of occurrence of adenoma of the islets as a consequence of pituitary lesions.

SUMMARY

Based on a survey of the literature and his own publications the author maintains that hypo- as well as hyperpituitarism do not cause simple micro- or macrosplanchnia but a characteristic pattern of dystrophy in various organs and tissues. The islet organ shows a hypertrophic tendency in hypo-, atrophy in hyperpituitarism. The metabolism of carbohydrates behaves correspondingly. Cases of insuloma of the pancreas combined with lesions of the anterior pituitary are discussed in this connection.

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Allergic Conditions in Hepatitis

By

B. O. C. PRIBRAM, M.D., F.I.C.S.

NEW YORK, N. Y.

ALLERGIC CONDITIONS

THE IMPORTANCE OF ALLERGIC CONDITIONS in abdominal diseases has not been sufficiently recognized up to now but it is an easy prediction that in the near future with increasing knowledge, the interest of the medical profession will be concentrating on this most interesting and fascinating field of new biological and clinical problems.

The results of many experiments point to the role the liver plays in allergic and anaphylactic reactions. In experimental histamine shock, Pick and Maunthner observed acute swelling of the liver which they believed to be due to a contraction of the muscular wall and the closing of valves of the hepatic veins. Histamine-like substances have been discovered in the hepatic veins (Manwaring and Dragsted, Lewis and Dale) which are supposed to play a role in allergic conditions while anaphylactic reactions failed to occur in dogs whose livers have been removed (Manwaring). There are also some clinical observations quoted in the literature pointing to the allergic character of some clinical features of liver troubles, and to the fact that liver syndromes may accompany cases of food allergy (Rowe, Ritz, Lichtwitz and Rowston).

However, the statement that there are some allergic conditions to be observed in the pathology of the liver does not cover the facts and does not do justice to the importance of this problem, which is to our belief a major one in the pathology of hepatitis. Moreover, allergic conditions play an important role in many abdominal diseases. The author has been interested in this subject for more than 25 years when analyzing allergic conditions in the pathogenesis of gastric ulcers and when developing the protein therapy for these conditions and giving intravenous injections of a non-specific protein as desensitizing treatment for gastric ulcers.

Recognizing and understanding of allergic conditions in abdominal diseases has proved to be a great

help in understanding many pathological features and also in finding ways for successful treatment. One cannot discuss special features in the liver without keeping in view the wider general aspect and outlook.

When giving in preliminary remarks a short survey of the meaning of the term allergy in abdominal diseases, we realize that a wider view of the term has to be taken and it is open to discussion whether the name allergy for these features is justified at all. The original conception was based strictly on the fact of a local inter-action of a specific antigen as an irritant, and an allergen as an anti-body. However, as in all definitions concerning biological reactions we see that with an increasing number of observations the primary orthodox conception no longer covers all the facts and no longer serves the purpose. We forget sometimes that definitions are primarily formulated only for the practical purpose of "filing" of observations and to put some order into their multitude. When sticking to these definitions too rigidly in order to preserve their orthodox character, there is, especially in the question of allergy, danger that facts and observations are eventually buried under the great and ever increasing number of new scientific names. The name "allergy" became popular and any practitioner understands the meaning; so it does not seem to serve any useful purpose to create further new names for the conditions to be described here.

We can no longer confine allergic conditions to the result of the well-known mischief, committed by some funny antigens, samples of which we find neatly collected in the magic test-boxes of Allergy Doctors. The biological problem lies much deeper. We must realize that practically everything in the surrounding world may become, under certain conditions, an allergen, provided that the victim is sensitized generally or partially against this outside irritant. In this way the "specificity" is partially conveyed from the allergen to the sensitized tissue or organ.

Long before allergy had been discovered and became

popular it was known by all practitioners that when an infection or intoxication had invaded the body, some tissues or whole organs, were left in a state of higher sensitiveness and irritability reacting to any new invasion in a way which we may call today "hyper-ergic." Such spots have been called in former times "Loca Minoris Resistentiae." Any kind of tissue having been the place of a toxic irritation or inflammation may remain in a state of higher sensitiveness and liable to react in a different way to all kinds of external damage or irritants. Scars in all tissues frequently respond to any changes in the atmospheric conditions with a kind of local reaction, increased tenderness up to real pain. This is so regular that such scars are sometimes considered by their owners as very reliable barometers.

Similar local reaction can be obtained by intravenous or intramuscular injection of a non-specific protein. From a purely clinical point of view it is difficult to see any essential biological difference between these reactions in a sensitized spot and an allergic reaction in the orthodox sense.

It seems rather useful, at least for practical purposes, to realize this similarity and to take a wider view as to the definition. According to estimates about 10% of the whole population show allergic symptoms to such a degree that sooner or later they have to consult a doctor. In some way the tendency to allergic reactions is inherited but the tissue or organ which is involved may vary considerably. While in about 50% allergic conditions can be found to be familial, in the other 50% allergic or hyper-ergic sensitiveness against something can also be acquired during lifetime. When going thoroughly into the history of the first reaction, we can easily find out that the first hyper-ergic reaction took place under special circumstances *leaving a certain biological mark.*

The skin of a person became sensitized against a certain scent resulting in rashes when even slight doses of this perfume came in contact with the skin. It was found out that the patient had been using this perfume previously for years without noting any undue reaction. One day, being in a summer resort, she was spreading this perfume over her neck before exposing herself to the bright sun-rays. The consequence was rash on the skin of the neck lasting for a few days.

Since that time allergy of a pronounced character remained against this scent even when it was used without exposing the skin to the sun-rays. What actually happened was that the additional irritation through the sun-rays on the first attack left a definite hypersensitiveness in the skin, perhaps in the way of decomposing the scent into some irritating products. Similar examples can be given for the origin of many kinds of hypersensitiveness. This holds good especially for food allergy.

A person suddenly acquired allergy against mushrooms while all his life he had eaten mushrooms in any quantity without showing any disturbances.

Another convincing example for the fact that food allergy can be acquired is the following:

A man of 56 enjoyed cucumber salad all his life as a favorite dish. One day he felt sick after a cucumber salad meal with signs of an intestinal intoxication. This

incident left a hypersensitiveness in his intestinal tract or perhaps his liver in a way that from this time even a small slice of cucumber salad invariably provoked the most alarming gastro-intestinal symptoms.

The specificity of allergen in the orthodox sense has to face another challenge by the observation that it can actually be replaced by another irritant which excludes a specific local immunity reaction altogether. A person may suffer from attacks of urticaria produced by poison ivy, primroses, strawberries, or other well-known potential irritants liable to cause an allergic reaction. There are many cases reported in which the pure imagination (delusion) of the presence of this antigen or hypnosis may cause in a psychic or nervous way an urticaria in this sensitized person as well. That is to say, the antigen can be replaced entirely by another irritant not only from a different chemical group, but by one which belongs, let us say, to a quite different biological sphere. The specific antigen to blame for these allergic conditions is entirely absent and no interaction between antigen and anti-body in the skin in an immunological sense can take place. Only the characteristics of a sensitized tissue remain.

This observation proves that the specificity of the sensitized tissue is sometimes more important than the specificity of the so-called antigen or irritant. Immunity and allergy are both expressions of the same biological process, i. e. defense against external damage, although both appear in exactly opposite phenomena. Immunity means that in a purely clinical sense no visible reaction at all takes place when a certain germ or toxin invades the body. Allergy means that an exaggerated, abnormally strong reaction takes place, giving the impression of a hypersensitiveness rather than of a successful defense measure.

The discovery of the amazing facts of immunity created the great hope and almost general belief that when a person has undergone a disease he will become to a certain degree immune from a further attack. Alas, a great deal of enthusiasm had to be given up, even for the small circle of infectious diseases where this rule holds good; on the contrary, experience has taught that the susceptibility for a disease increases for a second attack in the great majority. This holds true for all diseases of the respiratory tract, pneumonia, laryngitis, pleurisy, etc; it holds true for the kidneys, the nerves, the intestinal tract and last, but not least, for the liver.

When applying the term "allergy" for this sensitized state, we must realize that it is one of the most important features in general pathology. What are the characteristics of an allergic reaction in the liver? The pathologic changes can best be understood when considering them as an anaphylactic shock "en miniature," both in the extent as in the time of development.

Anaphylactic phenomena in the liver as observed in dogs are:

1. Contraction of the hepatic veins through closure of the valve mechanism.

2. Development of an acute liver-edema of more or less explosive character. This fleeting edema is certainly due to a sudden increase of permeability of not only the capillary walls and sinusoids but apparently of all cell membranes in the liver parenchyma. In experimental anaphylactic shock in dogs (Weatherford) it was seen that liver cells were invaded by red blood cells. We can, of course, speak of an increased epithelial phagocytosis. However, the fact remains that the membrane of the liver cells becomes easily permeable for other cells. We see further liver cells from broken-up cell cords within the lumen of blood vessels. This increased permeability of cell membranes involves a drop in the difference of osmotic pressure between cytoplasm and pericellular liquids.

Changes in the liver cells are: Edematous swelling and vacuolization, central necrosis, diminution of the caliber of the sinusoids of the hepatic lobules and of the efferent veins of the liver. Stasis of blood in the narrowed sinusoids and formation of hyalin plugs or thrombi. Manwaring believes that the narrowing of the hepatic veins is mainly due to pressure from the perivascular edema.

After injection of histamine fluid appears on the surface of the liver (Dale, F. Mauthner). When the surface of the liver of a dog is damaged through exposure and then the dog is allowed to drink water, one can observe that 6-10 minutes later water drops from the surface, often pinkish-stained through hemolysis, exactly as after injection of histamine.

A certain enlargement of the liver is physiologic. The considerable amounts of fluid absorbed from the intestines during meals and conveyed to the liver by the portal vein do not pass through directly into the circulation. They are retained by the liver and only gradually released on an equal level with the diuresis. No marked dilution of the blood even after the intake of large amounts of fluids can be observed.

Suppose a person takes with his meal a foodstuff which does not agree with him, or to put it in another way, to which he is allergic. In such a case we may observe an enlargement of the liver by far surpassing the above mentioned physiologic conditions. The liver may reach more than a hand's breadth below the costal arch. The consistency is soft and in contrast to acute congestion through heart failure, the liver is not or only slightly tender. The edematous fluid consists of water and a few electrolytes. The edema has a fleeting character and is readily reabsorbed into the capillaries in a very short time. This absorption is accelerated by intravenous injection of a 50% glucose solution.

Clinically, the patients complain of pressure in the epigastrium, flatulency, anorexia and sometimes nausea. Here is a brief description of such a case.

CASE REPORT

Mrs. A. S., 60 years of age, complained of discomfort

in the epigastrium and feeling of being blown-up, trouble which started two days before after a meal. She remembered that some time earlier she had had exactly the same symptoms, always following the intake of freshly baked warm bread. She had eaten it again two days previously. Ten days before she had had an attack of "flu" which made her feel ill and rather run down.

Upon examination the liver was found greatly enlarged, the right lobe reaching more than a hand's breadth below the costal arch. The consistency was soft. Urobilinogen in urine was greatly increased and bilirubin-reaction slightly positive.

Vidal's test: This was carried out with 200 ccm. milk given orally. The white cells dropped from 7,700 to 6,100 while eosinophiles rose from 5 to 9.6%.

Treatment: Intravenous injection of 10% of 50% glucose solution and 10 ccm. of 10% saline solution was administered.

Within 24 hours the size of the liver had already considerably diminished. After 48 hours, all clinical signs had disappeared and no enlargement of the liver could be stated. Patient felt hungry and perfectly well. Urobilinogen in urine was scarcely increased and the eosinophiles had dropped from 9% to 5%.

In most cases a desensitization of such patients can be obtained by intravenous protein-injections. This is the record of a man taken in 1922.

A man of 25 showed regularly pronounced allergic symptoms after the intake of eggs. Nausea, belching and feeling of being blown up. The liver was acutely enlarged and of soft consistency reaching one hand's breadth below the costal arch. This enlargement of the liver disappeared sometimes within a few hours. Desensitization through intravenous protein-injection (novoprotein) cured him completely from his allergic conditions.

SEROUS INFLAMMATION

Supposing the damage to the capillary walls through absorption or parenteral invasion of toxic products becomes more serious. In such a case the permeability of the capillary walls and cell membranes would increase and become permeable also for colloids. Krogh showed experimental evidence for the fact that the capillaries in a state of toxic paralysis become permeable also for substances as large as e. g. starch particles.

In liver pathology the effusion of serum albumin through such damaged capillary walls plays an outstanding role. This effusion, stainable with eosin, has a definite inflammatory character. It interferes with the normal blood supply and exchange of gas and other products of metabolism. Secondary cell damage in the form of cloudy swelling and degeneration, even necrosis, may result (Roessle, Eppinger).

The effusion in serous inflammation never reaches the amounts as in case of the fleeting edema. The liver is sometimes slightly enlarged or not at all. It is more a microscopic diagnosis than a clinical one. The effusion from the blood capillaries is followed by marked, though sometimes rapidly disappearing changes in the blood.

1. Relative increase in number of red cells (hemoconcentration).

2. Change in the albumin ratio. globulin

The most important point is that in contrast to the watery effusion of the fleeting edema, this *inflammatory effusion is not reabsorbed* into the bloodstream but slowly carried away with the lymph by the lymphatics. While in the case of a fleeting edema, *resstitutio ad integrum* without any trace can be observed within a short time, through the slow draining away of the effusion; here the course of complete recovery can be prolonged. Should this effusion contain irritant and toxic products, definite signs of irritation or inflammation can be traced along the route of absorption in the *whole lymphatic system of the liver*. This is a well-defined pathologic and clinical entity that the writer has called *lymphangitis hepatica*.

LYMPHANGITIS HEPATICA

ANATOMY (*operative findings*)

The liver is moderately enlarged. Glisson's capsule is turbid and there is a conspicuous subcapsular yellowish-gelatinous effusion. Freshly formed and very friable whitish adhesions can be seen between the capsule and the subcostal peritoneal wall. The lymphatic glands around the neck of the gallbladder and along the common duct are enlarged and hyperemic. Gelatinous effusion is often found here as well. The gallbladder is enlarged, the wall thickened, and the edematous serosa is hyperemic. When opening the gallbladder, the surgeon, not acquainted with this pathologic feature is surprised to find that the mucous membrane has a completely normal aspect. It is pale, not hyperemic, and does not show the slightest sign of inflammation. If stones are present, it is evident that they have nothing to do with the inflammatory process of the gallbladder which is exclusively confined to the *subserous lymphatic spaces* and the lymphatic glands.

It is an acute hepatitis, peri-hepatitis and peri-cholecystitis, a process which obviously originates in the liver spreading into the sub-capsular lymph spaces involving the lymphatics and glands around the gallbladder and in many cases reaching the lymphatic tissue of the pancreas, around which greatly enlarged lymph glands can sometimes be observed.

In order to understand the nature of this disease of the lymphatics, it is useful to bring it in connection with similar infections of the intra-abdominal lymphatic system, described by the author as *lymphangitis mesenterialis* and *abdominalis* including the so-called *lymphangitic form of appendicitis*. Since the first paper in 1925 the knowledge of this interesting disease has been considerably increased through many observations and also through experimental work of my associates and myself.

LYMPHANGITIC FORM OF APPENDICITIS AND LYMPHANGITIS MESENTERIALIS

When operating on some cases for acute appendi-

citis, most of them being young males up to twenty years of age, the following can be observed: A moderate amount of turbid peritoneal effusion confirming the diagnosis of an "acute abdomen." The appendix is edematous and swollen. However, when opening the specimen, one is surprised to find the mucosa pale and without any signs of an acute inflammation, proving that the inflammatory process *positively did not originate in the mucosa* as is the case in a common appendicitis, but is localized in the subserous lymphatic spaces of the appendix. It is what I have called the *lymphangitic form of appendicitis*. In some cases, apart from the acute inflammatory signs of the appendix wall, the peritoneum and mesenteries are reddened as in acute peritonitis. Large and acutely inflamed glands are found especially in the ileo-cecal angle. The glands are soft and friable. Microscopically, hyperplasia, edema and "signs catarrh" are found. Bacteriological culture from the peritoneal effusion or from the lymphatic glands remains sterile with few exceptions.

This form of appendicitis appears frequently in "epidemics" so that often several members of the same family, children and adults, are attacked. Surgeons usually accept this obviously puzzling observation as an expression of the rule of "duplicity." The fact is not puzzling at all when realizing that the infection in these cases is hematogenous and follows almost regularly an acute tonsillitis. It is an infection of the abdominal and mesenteric lymphatics and definitely does not originate in the mucosa of the appendix. Therefore, the distinction from the common appendicitis is essential.

The follow-up of these cases is interesting. There is a definite tendency to flare-up and in practically all instances these flare-ups are related to a flare-up of a chronic tonsillitis. These recurrences of abdominal attacks are independent of whether or not the appendix has already been removed. The clinical symptoms may be so alarming, so completely identical with an attack of acute appendicitis, that in some cases the surgeon may have his doubts whether the appendix has been indeed removed at the first operation.

The findings are as described: hyperemia of the acutely enlarged lymphatic glands of the mesenteries which themselves are found to be red as in a very acute inflammation. Prognosis is favorable but I have seen fatal cases.

It is noteworthy that bacteriologic examinations reveal sterility of the lymphatic glands in most cases. Only exceptionally were streptococci, staphylococci or coli found — an observation that, through its rarity, lacks significance. There are two possible explanations: Either it is a viral infection or the enlargement of the lymphatic glands is of an allergic nature. This concept is supported by some experiments (Fischer, Pribram and associates) in which an allergic lymphatic appendicitis and lymphadenitis could be produced in sensitized guinea pigs.

Whatever the true nature of the disease is, from

a practical point of view the observation is important that tonsillectomy in such cases has definitely proved successful. The flare-ups of the disease disappeared with the removal of the infected tonsils.

Application of our knowledge of this lymphangitis mesenterialis has proved very helpful in understanding the pathologic feature of lymphangitis hepatica. All our observations in the clinico-pathological complex of lymphangitis hepatica suggest that this disease too can best be understood by being included among the affections of the lymphatics of the organs of the abdominal cavity, the lymphangitis mesenterialis and abdominalis.

The perihepatitis which is a regular finding, originates in the liver and is not a primary inflammation of the liver capsule in the sense of a localized peritonitis without participation of the liver parenchyma. The liver capsule is an excellent protective structure and even a peri-hepatic and subdiaphragmatic abscess does not penetrate into the liver in causing a hepatitis. Clinically, lymphangitis hepatica runs the course of a chronic hepatitis with a pronounced tendency to flare-up which may be shown in moderately elevated temperature (99-101) in contrast to the high and swinging temperature in cholangitis. A slight degree of icterus is often present with definite increase at the times of acute flare-ups.

Relation to some focal infections, especially the tonsils, can almost regularly be observed. The majority of patients are young males between 20 and 30; this observation which is common also in lymphangitic appendicitis and lymphangitis mesenterialis may be explained by the fact that the lymphatic system is more developed and more irritable in young individuals. A constitutional factor is frequently observed: the disease may occur in more than one member of the family. Allergic conditions can frequently be observed and have their particular clinical significance.

We have recorded 25 cases altogether where the clinical symptoms and biopsy were characteristic as described above. They were 15 men and only 10 women, a fact which deserves attention because it is well known that cholecystic disease is otherwise much more common in women. Most patients were under 40 years of age, but histories of previous attacks were obtained in all instances. The youngest in the series of observations was a boy of eighteen. The constitutional "touch" of lymphangitis hepatica can best be illustrated by the fact that we had under our care three members of the same family, sister and two brothers, all persons of definitely lymphatic constitution with exactly the same clinical picture of hepatitis caused by focal infection in the tonsils: all of them were completely cured by tonsillectomy.

This is the characteristic case of a man who was a doctor himself.

CASE REPORT

The patient was 32 years of age and had suffered for years with liver troubles. Some enlargement of the liver

was stated by all observers with definite tenderness especially during the acute and subacute periods. No real acute colicky pains were observed, but rather slight periodic aggravations after relatively quiet intervals. Lack of appetite, constipation and increased intolerance for many kinds of food especially fat. Repeated cholecystography gave a fairly dense shadow of the gallbladder with sharp contours and with a good emptying. There were never any signs of stones. The shadow of the gallbladder was sometimes a little bit faint, but at other times quite normal. A real jaundice was never observed, but the urobilinogen in the urine was always increased. The patient used to go twice a year to Carlsbad or Vichy to undergo a strict cure, but he felt only slight improvement which did not last long.

When the patient came under my observation he was slightly jaundiced. Bilirubin was found to be present in the urine in traces, while the urobilinogen was greatly increased. The liver was enlarged and reached about three inches under the costal arch during inspiration. Consistency was harder than normal and slight tenderness felt everywhere in the epigastrium, in the gallbladder and over the right lobe of the liver. The gallbladder region was certainly not more tender than the whole liver. Bilirubin in the serum was slightly increased. The blood picture showed nothing abnormal. The tonsils showed signs of previous repeated inflammations and were slightly enlarged. A few drops of pus could be pressed out.

Upon inquiry, the patient gave the definite information that over a period of years every exacerbation was accompanied by a flare-up of his liver troubles; but he did not pay any attention to this, not realizing the connection. Temperature was now and then febrile. A few weeks before he had had another attack of tonsillitis which had caused an exacerbation of his liver troubles and also caused slight jaundice which he had observed himself. At the time he was terribly worried and convinced that he was suffering from carcinoma of the liver, a suspicion which seemed to be supported by the increase in size of his liver which he had also noticed himself, and the development of a slight jaundice around his scierae. In spite of treatment he had lost 14 pounds in weight over the past few months. His doctor, worried about the recent development, sent him to the hospital.

It was a great relief for the patient when I could explain to him the great probability of the connection of his liver troubles with a chronic focal infection — probably his tonsillitis, and then I advised tonsillectomy. This was performed with a striking result. A month after his dismissal from the hospital he came back for a re-examination. His general appearance was quite different than before the operation. He had a good appetite, could stand any type of food and instead of further loss of weight, had gained 4 1/2 pounds within three weeks. All signs of jaundice had disappeared. The liver was hardly increased in size. He emphasized that for years he had never felt so well as at present and that it was the first time in years that he was entirely free from all liver troubles. He could eat everything and enjoy his meals. In further follow up he never had any liver trouble.

In some cases an intimate connection between hepatic lymphangitis and an appendicitis (lymphangitic form) clearly could be observed, the appendix in a way forming a primary focus, the removal of which brought rapid improvement of the liver pathology. Similar cases are reported by other authors. One described by Saarroff may be quoted.

A five-year old boy — the age should be borne in mind — suffered with recurrent attacks of acute appendicitis, each attack being accompanied by enlargement of the

liver, bilirubinuria and almost acholic stools. All liver trouble disappeared completely after appendectomy.

What is the later course of such an lymphangitis hepatica? A certain damage to the liver cells may take place in the very beginning. This liver cell damage increases with the frequency of liver attacks and the toxic influence of the focal infection. Attacks of hepatic jaundice lasting for several weeks can be observed. The liver enlargement becomes permanent and the consistency harder. As in all forms of hepatitis, which last over a long period, while the same toxic cause persists, cell degeneration and cell necrosis parallels with an increase of fibrous tissue. Toxic cirrhosis may develop.

THE ROLE OF SENSITIZERS (FERTILIZERS) IN INFECTIVE HEPATITIS

Allergic conditions of the liver produced by all sorts of toxic products may, even in a latent state, facilitate and pave the way for a specific viral hepatitis. For a long time it was a puzzling observation in experimental medicine that one has considerable difficulties in producing a liver damage similar to the pictures we see in human pathology, e. g. when trying to produce cirrhosis of the liver by continuous administration of large doses of alcohol. However, we do succeed more easily in our experiments when, in addition to alcohol, we cause a second damage, e. g. by transmission of infecting agents. Many similar observations both in experimental and clinical medicine have led to the conception that at least *two factors* are usually necessary to cause a liver disease of the character of hepatitis, an experience which has been formulated in the following words (Hampson) "There is a seed necessary, a soil — that is the liver — and a fertilizer, so that the seed can take." Noel Fiessinger found the following words: "It is the first damage which suppresses the defense of the liver against the second attack."

We know a considerable number of such fertilizers or sensitizers, apart from alcohol. Arsenicals and other heavy metals, malaria, accumulated and repeated vaccinations, sulphamides, but also nutritional deficiencies (in vitamins and hypoproteinemia) and excess of fatty food.

The influence of alcohol as sensitizer in acute epidemic hepatitis could be established in two ways.

1. Alcohol may cause a relapse of hepatitis a considerable time after complete clinical recovery.
2. Alcohol may shorten the incubation period.

Many authors have reported convincing evidence for the first instance and for the latter, I am able to furnish an interesting observation.

A man with a fractured leg was in the hospital under my care and, lying in extension for seven weeks, he had no possibility of contact with any carrier of hepatitis virus. He had never received any blood or plasma transfusion.

He was put in a plaster cast and asked for a day's

leave to see his son who had his birthday and was taken ill with infective hepatitis. There was a slight epidemic, mainly amongst children, at the time with an incubation period of 22-23 days.

The patient stayed at home for two days and celebrated heavily with meals and alcohol. On the third day he returned to the hospital and felt all signs of indigestion after his heavy meals. Eight days after exposure, he developed acute icteric hepatitis.

This observation is very suggestive. The liver damage done in his days of celebration plus the exposure to the infected child obviously had caused the incubation period to come down to eight days instead of 22. This may also throw some light on other problems of hepatitis.

We have to state that generally there is only a small individual variation between the cases of hepatitis of one epidemic. A certain "team-spirit" can be observed between these patients who show more or less the same incubation period, the same prodromal symptoms and the same clinical course. On the other hand, there can be a *tremendous difference* between different epidemics. So it would be wrong, even when observing one epidemic of 500 similar cases to leap to general conclusions.

The difference starts with the mode of infection. In some epidemics, droplet and individual contact infection could be established beyond doubt, while in others, contaminated water or food had to be blamed and contact infection could be excluded. The clinical course also may show fundamental differences in different epidemics.

In some epidemics, especially in the group of the so-called serum hepatitis initiated by transfusion of infected pooled serum, *vascular symptoms* of the portal branches may appear right in the beginning. *Ascites* and *hemorrhagic diathesis*, due to venous stasis and portal hypertension, can be observed as early as in the first two or three weeks. In other epidemics, serious symptoms of the *central nervous system* may appear almost with the onset of the disease. These are the fulminant cases which frequently turn into yellow atrophy and which show a mortality up to 46%. No doubt these epidemics are caused by a virus strain with highly neurotropic properties.

In other cases, the gastro-intestinal symptoms stand in the foreground right at the beginning. No biphasic course is observed as is so characteristic in other forms. The first symptoms often start immediately after a suspected meal and continue until jaundice becomes visible. Obviously, this gives the impression of an intoxication rather than an infection and many experienced observers, like Eppinger, up until recently denied any infectious origin of this gastro-intestinal type.

The case described above may give us the clue for understanding and an acceptable solution. Supposing a person, having been infected with the virus of epidemic hepatitis, just being within the incubation period, is taken ill with an acute indigestion that causes a certain liver damage (allergic edema, serous hepatitis).

Not only might the incubation period be shortened but the viral hepatitis might break out which, without this secondary liver damage, perhaps would not have developed at all. He might remain a simple virus carrier as some blood donors prove to be who, although personally healthy, harbor the viruses with potential pathogenic properties and may infect the blood receiver. Given such circumstances we can easily understand that the symptoms of his indigestion, appearing right after the intake of the meal, might in one phase *pass into the outbreak of icteric hepatitis. The first symptoms we observe are not the symptoms of the viral infection; they are the symptoms of SENSITIZATION.*

A very banal comparison may help in understanding the process. Supposing we are about to catch cold, an acute nasal catarrh after exposure to cold and nasty weather. On coming home a few hours after exposure, we feel already the first signs of a soreness in the throat, and congestion of the nose which starts running. We can hardly imagine that the symptoms we feel are due to a rapid multiplication of a few germs we were about to inhale or that were living as saprophytes on the surface of our mucous membrane. What we actually feel is a sort of sensitization due to acute anoxemia, due to contraction of the capillaries, and the edema caused by an effusion through the damaged capillary walls. Only later on this sensitized tissue does the actual infection develop within the usual incubation period with the infecting agents penetrating into the deeper layers of the sensitized tissue.

When fully realizing the importance of the sensitizing factors in liver diseases the ways for prevention of any damage are clearly shown. Prevention of hypoproteinemia and vitamin deficiency has been generally recognized as an important factor in treatment of hepatitis. Avoidance of alcohol, heavy metals and sulfamide drugs in endangered patients and generally during an epidemic has to be stressed. Intelligent restriction of vaccination in patients where a latent liver damage can be assumed should be accepted as a reasonable rule.

In case of an acute indigestion or food allergy, some "emergency measures" may have full effect in preventing further damage: radical purgation with Epsom salts and a liver "cell-cleaning" by means of intravenous injection of 20 ccm. of 50% glucose solution right at the onset of the first symptoms may equal the effect of a washout of the stomach in case of poisoning. This discussion of the problems of sensitization should serve to make the practitioner "allergy conscious" when dealing with initial liver damage.

SUMMARY

1. Sensitization and hypersensitivity of organs and tissue structures play an important role in pathology

and clinic. It is open for discussion whether the term allergy is adequate for these conditions, but it seems to be rather more practical to widen the term allergy over its original orthodox meaning than to create new names.

2. Since the liver plays a main role in food-allergy and all forms of acute indigestion, allergic conditions in the liver are frequently observed. They can be considered as an anaphylactic reaction "en miniature." While a certain increase of the size of the liver through absorption and retention of water is physiologic during digestion, food allergy may lead to an explosive edema with considerable enlargement of the liver.

This edema, consisting of water and a few electrolytes, has a fleeting character and may be readily reabsorbed into the blood capillaries within a short time.

3. In case of more serious toxic damage to the walls of the capillaries, they may become permeable also for colloids. Serum albumin and toxic products of metabolism or infections may penetrate as well and may form an effusion of inflammatory character in the pericapillary spaces. This effusion is not reabsorbed directly into the blood stream any longer but is carried away with the lymph by way of the lymphatics.

4. The whole lymphatic system of the liver may show marked signs of irritation through absorption of such an effusion of toxic-septic character. The liver surface becomes turbid, a whitish-gelatinous effusion may appear under Glisson's capsule, the lymphatic glands along the common duct and the neck of the gallbladder may become hyperemic and enlarged. The wall of the gallbladder may become edematous while the mucosa is found to be normal, proving that the process of inflammation is confined to the subserous lymphatic spaces. This pathologic change is characteristic of a well-defined disease which has been called *lymphangitis hepatica* by the writer.

5. This disease can best be understood within the frame of lymphangitis mesenterialis and abdominalis, and the lymphangitic form of appendicitis. Relation to focal infections is often marked.

6. Sensitization of the liver through all sorts of damage, alcohol, arsenicals and other heavy metals, abuse of sulfa-drugs, hypoproteinemia, excess of fatty food, etc. frequently play an important role in the development and pathology of hepatitis. Instances of cases are given that may help understanding of some features in the clinic of hepatitis. Sensitization of the liver may shorten the incubation period of epidemic hepatitis in some instances; in a virus carrier, it may actually cause the outbreak of hepatitis. An acute indigestion may shorten the incubation period, thus giving the clinical impression of an acute food poisoning rather than of an infection.

Tumors Arising in Brunner's Glands

By

ABRAHAM O. WILENSKY, M.D.,

NEW YORK, N. Y.

TUMORS OF THE DUODENUM were practically unknown before the advent of roentgen examinations and those few which were found resulted from post-mortem examinations. Almost 100 years ago, Cruveilhier (9) described a case of adenoma of the duodenum. In 1861, Rokitsanski (26) confirmed the presence of benign tumors in the duodenum. Another case was reported by Salvioli (29) in 1876. In 1897, Thompson (31) found a tumor in the first portion of the duodenum during the course of dissection of a cadaver. The tumor was as large as a nut and hung from a thick pedicle; histologically this was an adenofibroma. In 1899, the statistical information of tumor of the duodenum was recorded up to that time by Heurtaux (16); additional cases were reported, and the subject was brought up to date in 1917 by King (19). The latter gathered a total of 119 cases of benign tumor of the intestine, of which only five were in the duodenum.

With the advent of the roentgenological period the following cases were published and were collected by Le Bigot (21): Russell and Carman (28), Meisel (23), Van Tienhoven (32), (1921); Klose and Gotze (20) (1923); Camp (8) (1924); Akerlund (1), Willis and Lasersohn (33) (1925); Golden (12) (1928); Bernstein (3), Judd (18), Balfour and Henderson (2) (1929); Waters (34), Bookman (6) (1930); Finney and Finney (11), Brdiczka (7), Pohlandt (24) (1931); and Seneque, Gutmann and Dicles (30), and Gutmann (14) (1935).

The classification of the 30 cases collected by Le Bigot (21) is as follows:

hemangioma	2 cases
adenoma	6 cases
polyp of mucus cells*	1 case
papillary adenoma	2 cases
papilloma	6 cases
tuberculosis	2 cases
myoma	3 cases
fibromyoma	2 cases
"benign" tumor*	6 cases

* no further anatomical diagnosis is available.

In addition to these, Pack and McNeer (25) have unpublished data of 16 collected cases of adenoma of Brunner's glands without cystic formation or mucinous retention which they have gathered from the literature (Ref. no. 7 in Booher and Pack's paper: vide infra.).

The following personal case of adenoma of Brunner's glands in the duodenum is reported.

CASE REPORT

J. E. Pk E. The patient, a 45 year old married man, who complained for the preceding six months of rather slight symptoms of eructation and belching. For the last two weeks only of this period he had vomited and the vomitus contained blood. The stools were also black. The work-out was not definitive until the essential roentgenological study (Snow) showed a polyp in the first part of the duodenum. There was a weight loss of 15 pounds. The physical examination of the patient was otherwise negative.

The patient was thereafter explored: a polyp measuring two inches long by one inch in diameter was found hanging on a fleshy stalk about 1 1/2 inches long. The tumor was ablated by integrating the latter excision in the procedure of a Finney pyloroplasty.

An uninterrupted recovery and convalescence followed and the patient was discharged well. The follow-up record shows an absence of any post-operative symptoms.

During the course of the operation, soft masses were palpated in the colon which were interpreted to be other polypoid structures. Nevertheless it was deemed advisable under the circumstances to go after them. Fortunately there are no symptoms which could be referred to them.

The specimen was examined by Dr. Schiffrin, whose report is as follows:

Macroscopic:

The specimen consists of a polypoid mass the size of a large butter nut. It measures 3x3x2 1/2 cm. Its pedicle measures 1 1/2x1 cm. Its surface is slimy and shaggy. A sagittal section shows the mass to consist of homogeneous and grayish pink tissues containing somewhat firmer pale areas. The tissue is scrapable but not friable.

Microscopic:

The tumor mass consists of numbers of regular glands lined by regular columnar cells with abundant pale and finely granular cytoplasm and regular usually basally situated nuclei. The basal membranes of the glands are sharply demarcated. In occasional sites there are present adjacent to similar regular glands, a number of cells which are polygonal and succulent with abundant pale and finely granular cytoplasm. The nuclei are small, dense and regular. Together they form groups of cells without glandular arrangement. There is no nuclear atypism and no mitoses are seen. The base of the pedicle consists of wavy bands of fibrous and smooth muscle tissue and shows no tumor infiltration.

Diagnosis:

Fibroadenomatous polyp (benign) arising from Brunner's glands.

ANATOMY

Brunner's glands are limited to the proximal part of the duodenum and are found in the submucous areolar tissue. They are largest and most numerous near the pylorus, and form an almost complete layer in the first and second parts of the duodenum, from which point they diminish in number and disappear at the duodeno-

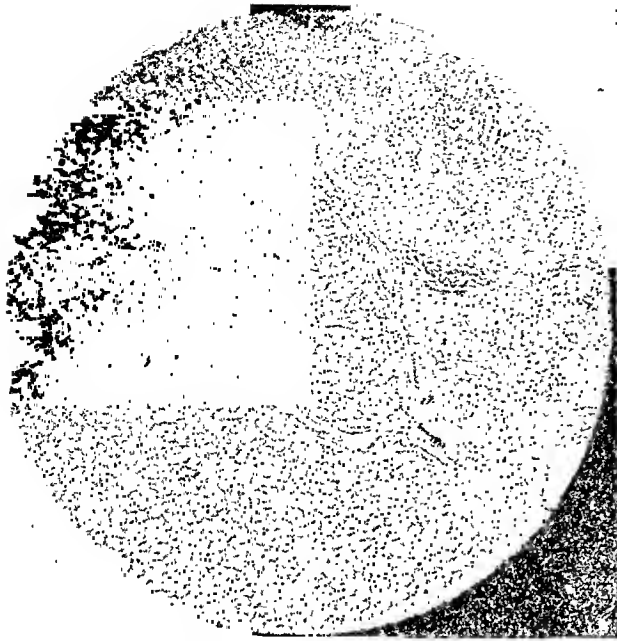


Fig. 1. — Adenoma of Brunner's glands; low power magnification.

jejunal junction. They are small compound acinotubular glands consisting of a number of alveoli lined by short columnar cells, and they empty by a single duct on the inner surface of the intestine. (Gray's anatomy) (13).

The Brunner glands resemble the pyloric gastric glands. Their secretion is alkaline, they secrete a mucoid fluid, and the latter contains a weak proteolytic ferment. (Best and Taylor (4).

ETIOLOGY

Inasmuch as this part of the alimentary canal is a very active one, it is rather unexpected that tumors of the Brunner's glands do not occur more frequently. The neoplastic change, because of its essentially benign nature and the fact that the structure reproduces the glandular architecture of the normal gland, must undoubtedly have dominating relationships to the functional activity of the gland rather than to a true neoplastic mechanism. This seems to be borne out by the frequency with which cystic disease takes place.

Robertson's discussion (27) of the cellular and resultant pathological changes is as follows:

"The outstanding characteristic of the glands is their comparative freedom from influences which ordinarily affect secreting tissues. General toxemias, starvation states and dietary deficiencies apparently leaves them unscathed. The cells at times have an almost clear protoplasmic content, staining only faintly or not at all with ordinary dyes or even with specific mucin stains, and the ducts are free from stainable substances. This condition has been pointed out as evidence of increased function, but I have observed it in the region of duodenal ulcers and other inflammatory processes in the mucosa of the duodenum. Occasionally there is a stasis of secretion, with dilated ducts and acini. In some cases this is evidently because of obstruction to the ducts; it has been ob-



Fig. 2. — Adenoma of Brunner's glands; high power magnification.

served in the region of invading or metastatic tumor nodules and on the margins of chronic or healed ulcers. Such a condition may lead to cyst formation, in which acini or even an entire lobule may be dilated and contain a mass of cell detritus mixed with varying amounts of mucin . . . More rarely occur large cysts reaching several millimeters in diameter and producing easily observable nodules in the duodenal wall . . . These cysts are lined with low cuboidal cells, and the lumens are largely free from stainable substances."

Hartz and van der Sar (15) take a somewhat different viewpoint regarding proliferative activity in Brunner's glands. They associate the latter with the presence of inflammatory changes in the surrounding tissues, as a result of which the glandular epithelium reacts in much the same way that it would elsewhere. Under such circumstances Booher and Pack believe that there should be more evidence of hypersecretion and subsequent retention, in view of the many stimuli to which this part of the upper intestine is subject.*

Clinically, cystic dilatation in Brunner gland tumors and frank cysts (enterogenous cyst of the duodenum) apparently occur frequently in relation to the total number of cases of Brunner type tumors reported in the literature. The situation regarding cystic tumors

*I am indebted to Booher and Pack's paper (5) for this part of the discussion.

of the duodenum was recently reviewed by Booher and Pack (5). Thirteen such cases were reported, including one case of their own. Six of these patients survived operation (operative mortality 45.4 per cent).

From the descriptions given by Booher and Pack (5), it seems likely that several different etiologically produced cysts were present in their cases. They discuss the opinion of Lewis and Thyng (22) in which some relation is assumed between these cysts and intestinal diverticulae with the possibility of misplaced or accessory pancreatic tissue. In this regard the possibility of an origin from a high Meckel's diverticulum is dismissed. They also discuss the theory of Hughes-Jones (17) of a possible origin in sequestered epithelium as an origin for these enterogenous cysts. At any event, it seems that the cases in their series do not all arise in Brunner's glands.

A tendency to malignant changes was noted histologically in two of the papilloma cases in the series of Le Bigot (21). Except for this there is practically no reference to malignant neoplasia arising in Brunner's glands. In discussing carcinoma arising in the papilla area of the duodenum, Ewing (10) describes the histological structure as "commonly that of a cylindrical-cell adeno-carcinoma derived from the intestinal mucosa. An origin from Brunner's glands has been suggested by Orth (35) . . ." This seems rather far fetched to me, because the papillary area is distant from the area of the bulk of the Brunner's glands, and because of the dearth of reports of cases of carcinoma definitely assigned to an origin in these glands.

There seem to be many similarities in these abnormal manifestations and changes in cellular activity and structure to those so commonly seen in the thyroid gland. Cystic changes, adenomatous hypertrophies, and distinct benign tumors of adenomatous structure and architecture are quite common in the thyroid gland with an occasional malignancy, and are counter-parts of similar manifestations and structural change in the Brunner glands. The differences in clinical symptomatology are not difficult to explain, (1) because of the greater importance and more easily recognizable symptoms of thyroid disease, and (2) because of the lesser importance, possibly, of the function of the Brunner glands. The differences in clinical symptomatology the latter are easily lost in the general body economy. Symptoms of the latter diseases are, therefore, almost always of a mechanical nature either because of magnitude of the tumor, or because of prolapse of a pedunculated tumor into the pylorus, in either case with symptoms of some form of pyloric stenosis. All of this seems to be confirmed by the fact that many of the reported Brunner gland tumors are postmortem findings without any demonstrable clinical status during life.

SYMPTOMATOLOGY

The manifestations of Brunner gland tumors are

rather of a casual nature as a rule and those of many observed cases usually labeled as hyposthenic "dyspepsia." In such cases the symptoms may be mild or severe. Ordinarily these symptoms are not characteristic, consist in the main of many degrees of pain which have no relation to the taking of food. The definite signs are only demonstrable by X-ray study and by the visualization of circumscribed homogenous lacuna like spaces in a frequently dilated duodenal bulb. Occasionally it is possible to demonstrate the prolapse of a pedunculated mass backwards through the pylorus. This picture must be differentiated from retroduodenal lymph gland enlargement.

The observed complications are (1) some form of pyloric obstruction and (2) various grades of hemorrhage. In one reported case the latter was the cause of death. In one case reported by Le Bigot (21), the Brunner tumor was found unexpectedly during the course of operation for a callous duodenal ulcer. In another case, a gastritis was said to coexist.

When there are signs of pyloric obstruction X-ray visualization commonly succeeds in demonstrating the presence of a polypoid tumor prolapsing in retrograde direction through the pylorus.

TREATMENT

When provocative of clinical symptoms which call for treatment, surgical removal of these tumors is the only available method. Enucleation of the tumors involves opening of the duodenum with subsequent plastic repair of the duodenal wound with due regard to the prevention of any subsequent stenosis (e. g., by transverse closure of a longitudinal incision). Ablation of a pedunculated growth is the simplest of the procedures. In my case, it was easily feasible to interpolate the ablation in the course of a Finney pyloroplasty technic, and it seems to me that this method, when possible, is ideal. In any case, the procedures should relieve any symptoms of pyloric obstruction.

RADIATION THERAPY

There are no data available for the effects and/or the results of radiation therapy.

SUMMARY

The literature regarding tumors arising in Brunner's glands of the duodenum consists of 46 cases of benign solid tumors to which one personal case is added. These are reviewed. There are also instances of cysts arising in these glands. No instances of malignant transformation are recorded. The tumors are frequently pedunculated and commonly give symptoms of pyloric obstruction. They can only be recognized on roentgenological study. The pertinent facts regarding etiology, pathology and classification are discussed. Treatment is necessarily surgical.

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Editorial

THE IDEAL OF PERFECT NUTRITION

N PHILLIP NORMAN, M.D., consultant nutritionist for the New York City Departments of Health and Hospitals, who with James Rorty wrote the semi-popular book, *Tomorrow's Food*, continues to express his opinions with respect to how American nutrition may be improved.* His book, which was accorded favorable criticism in this Journal, has exerted a more or less wide-spread influence on the profession as well as the public. The general attitude taken by Norman is that the profession of medicine still clings to its static attitudes based on pathology and illness and neglects the study of exuberant health. He states:

"The Medical Profession as a group is preoccupied with the profit potentialities of miracle drugs. If they knew as much about health as they do about illness, they would serve the public more constructively."

As a matter of fact, there are few physicians who would not take a vital interest in "health" if they could catch Norman's vision of what the term implies. Health, unfortunately, is indefinable and has remained a mythical entity without convincing symbolism. Norman undoubtedly believes that "proper" nutrition is capable of conferring upon an individual or a group, in due time, a superlative degree of fitness capable

of relative immunity to infections and to the terrible degenerative changes so common now among older persons. He enumerates several points of attack on our present system of nutrition, some aimed at harvesting, storing, handling, processing and cooking of food products and still others dealing with soil fertility, seed culture and horticulture. Norman has a definite "vision" and with it a suitable dynamism for propaganda of an intelligent type.

Vested interests, of course, constitute the chief obstacles in the pathway of the noble experiment, yet no intelligent person will deny that the recommendations set forth are highly desirable, even though not all students are convinced as yet that superlatively good nutrition would be capable, even if it were accomplished, of producing the degree of general well-being indicated.

Nevertheless, a careful study of the English authors who recommend natural composts for fertilizing purposes, particularly McCarrison and Howard, and of the experimental work of Maynard, Albrecht, Brody and others in this country, leaves one convinced of several facts. One fact is that until proper soil fertilization is practiced, we shall not be able to obtain from food (nor from artificial vitamins) the strongest known impetus to health. A second fact is that where "pedigreed" food products have been eaten under proper conditions of cooking, a most *amazing* degree of health

*Norman, N. Philip: Fundamentals of Nutrition for Physicians and Dentists. Am. J. Orthodont. and Oral Surg., Nov. 1947, Vol. 33, No. 11, pp. 780-785.

has been obtained both clinically and in experimental animals. It is not too much to say that such nutrition has been proved capable of *banishing disease of all kinds and of conferring a vigorous old age*. As Minot has recently indicated, the most important research today is nutritional research. Nobody knows the breadth, depth or extent of the benefits in store for mankind as a result of the patient, laborious efforts of our nutritional experts.

I think the best efforts of us all should be dedicated to what Norman has in mind. There are countless hurdles in the path. Vested interests will fold up only on public demand. Education alone can create a suitable public reaction. The *ideal of perfect nutrition* is the most dynamic concept before the profession today. Its realization probably will require, not a decade, but two or three generations.

BEAUMONT S. CORNELL, M.D.

Abstracts Of Current Literature

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SURGERY

KENNEDY, C. S., REYNOLDS, R. P., AND CANTOR, M. O.: *Gastric stoma after partial gastrectomy*. (Surgery, V. 22, p. 41, 1947).

In gastrojejunostomy the stoma should be of such diameter as not to exceed that of the lumen of the jejunum. The passage of food from the stomach is frequently delayed even in the absence of stomal edema. This longer gastric evacuation time of course makes it necessary that the patient be cautioned against eating too much solid food at one time and too rapidly. The absence of sphincteric control permits the evacuation of liquids at a rate which may be too rapid to permit accommodation by the jejunal loop and thus give rise to epigastric pain.

The jejunal wall as well as the residual gastric wall dilate so that eventually the capacity of the stomach to retain food is increased. The stoma becomes overlapped by gastric muscular tissue so that in time there is developed a sphincter-like action.

WERBEL, E. W., KOZALL, D. D., AND MEYER, K. A.: *Surgical sequelae following recovery from a perforated peptic ulcer*. (Surg. Clin. N. Amer., p. 93, Feb. 1947).

This study was made on 239 patients with peptic ulcer whose history showed a previous perforation and who, at the time of the study, had ulcer complaints. Intractable abdominal pain was a major finding in 86 per cent of these cases. Hemorrhages were shown by 34 per cent of the cases. Evidence of re-perforation of the ulcer (same site?) was obtained in 17 per cent of the patients. Of the patients with re-perforation who were admitted to hospital, 30 per cent had some form of gastric surgery performed in addition to the perforation closure. Gastric resection, etc., was not required by most patients at the time of the first perforation since the incidence of re-perforation was not high enough to justify it.

PACK, S. T., MCNEER, G. AND BOOHER, R. J.: *Principles governing total gastrectomy — report of 41 cases*. (Arch. Surg., V. 55, p. 457, Oct. 1947).

This series includes 41 patients who underwent the operation for total gastrectomy. In only three patients was the lesion benign, in the remaining 38 patients the resection was for malignant lesions. In each patient the stomach was removed completely, together with all adjacent lymphatic tissue. In 25 patients early post-operative feeding was carried out through a nasal Levine tube while in the remaining 16 patients an ileostomy was used. In the first group there were five deaths, in the second group four deaths. The authors feel that while a higher nutritional state can be maintained by tube feeding, the presence of the tube in the nasopharynx is a bad feature and that the tube should be withdrawn before the tenth day. The operative mortality was 31.7 per cent. The average survival was 18 months but in patients without nodal involvement at time of operation it was 26.3 months. Five of the patients with cancer who showed no nodal involvement survived more than three years.

EXPERIMENTAL MEDICINE

PHYSIOLOGY

THOMAS, J. E.: *The intestinal pH threshold for regulation of gastric emptying*. (Federation Proceed., V. 6, p. 214, March, 1947).

Experiments were performed on unanesthetized dogs to determine the pH threshold for inhibition of gastric emptying. In some experiments the volume and pH of intestinal drainage material (via intestinal fistula) were measured after intra-gastric administration of acid solutions buffered to pH 1.5-1.8 with gastric mucus or egg albumen. In other experiments, graphic records of gastric motor activities were made and the influence of feeding and intestinal instillation of acid solutions determined.

Above pH 3.0 in the intestine there was no influence on gastric motility; motility decreased when the intestinal pH fell below 3.0 and was abolished below pH 2.0. In the absence of other stimuli an intestinal pH of 3.0 or lower is therefore required to modify evacuation time of the stomach.

VAN LIERE, E. J., NORTHROP, D. W., AND STICKNEY, J. C.: *The full effect of hemorrhage on intestinal absorption of chloride in the presence of sulphide.* (Proc. Soc. Exp. Biol. Med., V. 66, p. 260, Oct. 1947).

Previous work has shown that sulphate and certain other anions of the lyotropic series as well as hemorrhage of approximately 3.2% of body weight favor the absorption of sodium chloride from the dog intestine.

In order to study the combined effects of sulphate and hemorrhage, 15 dogs were bled 3% of their body weight. Four hours after recovery an intestinal loop approximately the full length of the ileum was washed and filled with equal parts of isotonic sodium chloride solution and isotonic Na_2SO_4 solution. After 40 minutes the contents were measured and analysed for chloride and sulphate. A group of 14 control dogs was treated similarly without having previous hemorrhage. Both groups of dogs showed marked absorption of chloride and fluid, with a concentration of sulphate in the remaining water absorption over that of sulphate. The rate of chloride absorption was slightly greater following hemorrhage but was not statistically significant.

ADOLPH, E. F.: *Urges to eat and drink in rats.* (Am. J. Physiol., V. 151, p. 110, Nov. 1947).

Albino rats were given food containing cellulose, kaolin, or water so that the bulk exceeded that of the more concentrated foods of the control period. Roughage to the average of 8% of their body weight and water up to 125% per day were consumed. When cellulose or kaolin diluted the food, the animal ingested more bulk but stopped before it had ingested a full quota of nutrients. Apparently one factor is a limited ability of the alimentary tract to handle the roughage. When diluted with water, food was taken in volumes which satisfied the calorie requirements without having the upper limit fixed by the maximal rate of excretion of water through the kidneys. This held true until only 2% of the total intake was solids, the remainder being water.

The water intake was modified by the food intake, so that if the nutrients were diluted with kaolin or limited in amounts, the ad libitum intake of water was correspondingly reduced.

PATHOLOGICAL CHEMISTRY

GRANICK, S. AND MICHAELIS, L.: *The presence of ferritin in the duodenal mucosa and liver in hemochromatosis.* (Proc. Soc. Exp. Biol. Med., V. 66, p. 296, Nov. 1947).

Ferritin is a normal iron storage protein of the body and has been considered to function in the regulation of iron absorption from the intestine. It has often been suggested that in hemochromatosis there is a defect in the mechanism governing the formation of ferritin in the duodenal mucosa. In a case of hemochromatosis reported here ferritin was found in the liver and duodenal mucosa. The blood picture was normal and the serum iron was high, indicating that iron transport was adequate. The authors conclude that the cause of hemochromatosis is not in the nature of a defect in ferritin formation in the duodenal mucosa.

COHN, P. C. AND THOMPSON, F.: *The serum protein fraction responsible for the thymol turbidity test.* (J. Lab. Clin. Med., V. 32, p. 314, March 1947).

MacLagan originally believed that a gamma globulin was implicated in the thymol turbidity test for liver dysfunction which he devised. The authors however find that a beta globulin is involved. Electrophoretic studies on serum with high thymol turbidity values showed high beta globulin levels. Electrophoretic studies on serum residue after removal of the thymol precipitate showed the beta globulin fraction to have been reduced to normal levels; studies on the precipitate showed a single protein with an electrophoretic mobility characteristic of normal beta globulin.

The beta globulin fraction is known to be lipid-containing, but the total serum lipids did not appear to be related to the thymol turbidity. A serum from a case of lipoid nephrosis with cholesterol value of 1400 mg. per cent gave a negative thymol turbidity test.

YOUNG, N. F., COLLIER, V., AND HOMBURGER, F.: *Arginase and catalase activity in liver of patients having benign and malignant gastric lesions.* (Proc. Soc. Exp. Biol. Med., V. 66, p. 323, Nov. 1947).

Studies reported in the literature have shown that in patients with cancer of the gastrointestinal tract there was invariably a concomitant impairment of certain liver functions. In rats and mice with a wide variety of tumors there has been reported a distinct decrease in liver catalase activities.

In the present study liver biopsies were made on 16 patients with malignant gastric lesions and 11 patients with benign gastric lesions (ulcer). The catalase and arginase activities of the liver sections showed comparable results in the two series of patients. While in animals with transplanted or spontaneous tumors the tumor appears to produce systemic effects in the host, in humans with gastric tumors these systemic effects remain to be defined more clearly.

PATHOLOGY

CHESTER, A. AND TISLOW, R.: *Oral efficacy of BAL in protecting rats against alloxan diabetes.* (Science, V. 106, p. 345, Oct. 1947).

BAL, or British anti-lewisite, was developed as a defense against war gases and has been found very

promising in cases of arsenic, lead and heavy metal poisoning. Chesler and Tislow found that intravenous injection of BAL could protect against experimental diabetes produced with alloxan and reduce the lethal effects of alloxan by fifty per cent. When given orally in much higher doses they found that BAL was also effective in protecting rats against alloxan diabetes.

LILUM, R., MADDOCK, S., AND JENSEN, I.: *The experimental production of acute pancreatitis*. (Federation Proceed., V. 6, p. 395, March, 1947).

Obstruction of the pancreatic duct of the active gland has been suggested as the etiologic factor in acute pancreatitis. Pilocarpine, eserine, acetylcholine and secretin were used to stimulate the pancreas in cats with either pancreatic duct ligated or duct patent. Animals were sacrificed 24 hours to 7 days later.

In cats with duct ligated and gland stimulated a uniform finding was that of pancreatic fat necrosis. The most extensive damage was produced when the pancreas was stimulated after a meal. Secretin was more effective than the other drugs in producing the pancreatitis.

The authors conclude that in humans obstruction of the pancreatic duct when the gland is secreting, as after a meal, results in pancreatitis. The influence of alcohol is believed to be indirect through activating pancreatic secretion by the gastric HCl produced by alcohol stimulation. Obstruction in man of the pancreatic duct may be due to calculi, ascaris, spasm, edema, or a tumor.

IVY, A. C. AND COOKE, A.: *An attempt to produce malignant transformation of gastric ulcers in rabbits: a preliminary report*. (J. National Cancer Inst., V. 7, p. 345, April, 1947).

In rabbits the excision of gastric mucosa with continued feeding of the rabbit's usual rough diet leads to an artificial "chronic" gastric ulcer. The authors thought that the chronicity of the ulcer would favor exposure to carcinogens administered orally and that the overgrowing mucosal edges seen in these ulcers would favor neoplasia. Rabbits with these chronic ulcers were given 15 milligrams of 20-methylcholanthrene daily. In domestic rabbits no detectable changes in the ulcer were noted after 3.5 to 5.5 months. However, in wild rabbits similarly treated, formation of epithelial cysts were noted in three of four animals after five to 13 months. No neoplasms of the intestine were noted in any of the rabbits after feeding the methylcholanthrene for as long as 18 months: this was in contrast to the findings of numerous small intestinal tumors in mice fed this carcinogen.

P. F. UNDERHILL

PERRY, T. T.: *Role of lymphatic vessels in the transmission of lipase in disseminated pancreatic fat necrosis*. (Arch. Pathol., V. 43, p. 456, May, 1947).

The author concludes from experiments on rats that in cases of disseminated pancreatic fat necrosis

following pancreatic injury there may be transmission of lipase by the lymph channels. Conclusions are based on experiments in which intraperitoneal injections of pancreatin solution and graphite suspension were made. Multiple areas of fat necrosis were found at postmortem in both abdominal and thoracic cavities. These areas were closely associated with graphite-delineated lymph channels.

P. F. UNDERHILL

METABOLISM AND NUTRITION

SMART, G. A., MACRAE, T. F., BASTENIE, P. A. AND GREGOIRE, P. E.: *The effects of food supplements on poorly fed workers in Brussels in January, 1945*. (Brit. Med. J., Jan. 10, 1948, 40-43).

Roughly half a group of 18 poorly fed workers were given a daily nutritious supplement in addition to their regular meals, the others acting as controls and it was found that the addition of the food supplement increased the weight, improved the nitrogen balance, strengthened the grip of the right hand as estimated by a dynamometer and, interestingly, decreased the duration of the irritability contraction of the biceps muscle in response to pinching. Unfortunately it was not possible to allocate to any one type or to any particular types of food supplement credit for the physiological improvements noted.

VAUGHAN, J.: *Anemia associated with trauma and sepsis*. (Brit. Med. J., Jan. 10, 1948, 35-39).

This is a presentation of the metabolic characteristics of the anemia associated with sepsis and that associated with trauma. Both anemias may depend upon a disturbance of hemoglobin synthesis, affecting chiefly the globin element. The globin deficiency depends on a wide disturbance of protein metabolism due to the action of breakdown products liberated from the injured tissues, and due also to the need of injured tissues for special amino-acids. Cobalt may be concerned in this chain of events. A high protein diet and careful nursing are two requisites in clinical treatment.

HAMIL, B. M., CORYELL, M., BODERUCK, C., KAUCHER, M., MOYER, E. Z., HARRIS, M. E. AND WILLIAMS, H. H.: *Thiamine, riboflavin, nicotinic acid, pantothenic acid and biotin in the urine of newborn infants*. (Am. J. Dis. Child., Oct. 1947, V. 74, No. 4).

Estimation of the daily excretion of the vitamins noted in the title indicated that secretion into the urine was high during the first three days when the loss of weight was rapid and the intake of vitamins small. As the supply of breast milk increased, excretion of vitamins in the urine continued to decrease. The large amounts of excreted early in life apparently represent tissue storage during intra-uterine development and reduction in the stores in response to changes resulting from the transition to extra-uterine environment.



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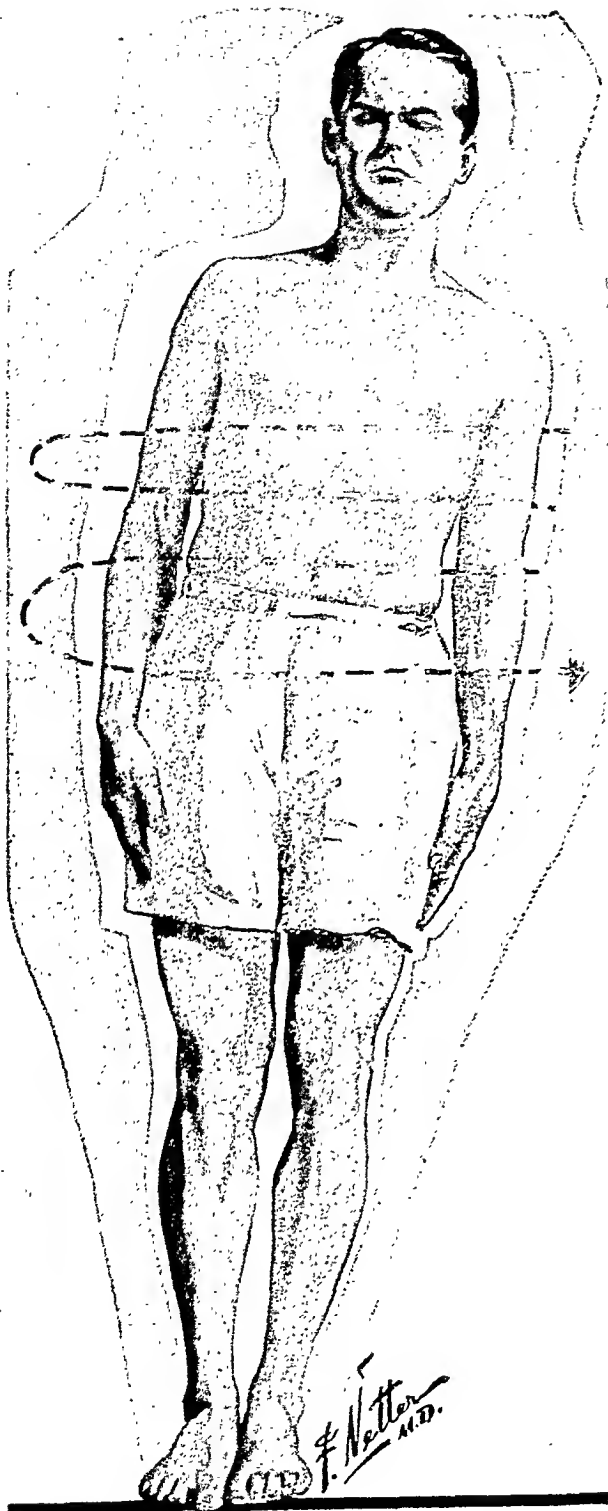


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*Krasno, L., Karp, M., and Rhoads, P. S., (1948), Inhalation of Dust Penicillin, Ann. Int. Med., 28: 607-617, March.



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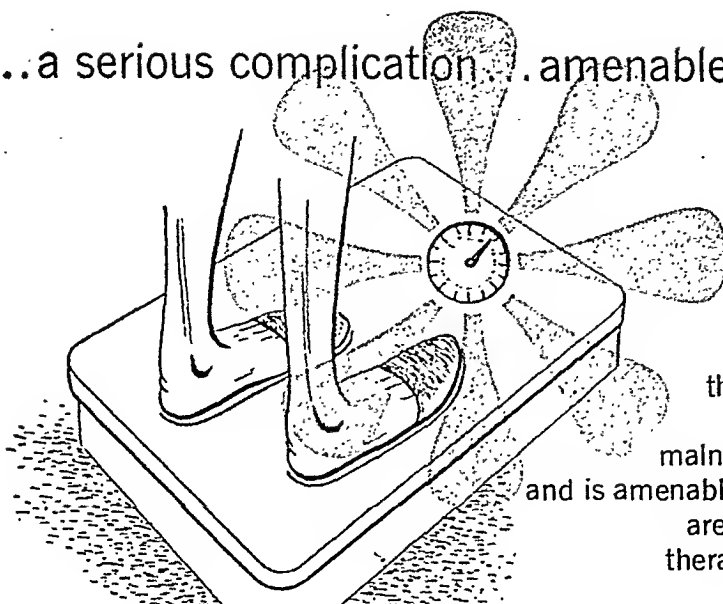
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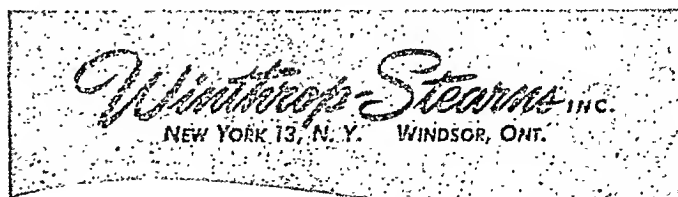
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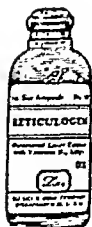
1. Sprinz, H.: *Med. Clin. North America*, 30:363, Mar., 1946.
2. Kozoll, D. D., Hoffman, W. S., Meyer, K. A., and Garvin, Thelma: *Arch. Surg.*, 53:683, Dec., 1946.



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The Genus *Shigella* and Shigellosis

By

ERWIN NETER, M.D., F.A.P.H.A.

BUFFALO, N. Y.

INTRODUCTION

BACILLARY DYSENTERY is an important infectious disease affecting man in almost every part of the world. The malady is caused by members of the genus *Shigella*. Occasionally, microorganisms belonging to this group of bacteria are responsible for diseases other than dysentery. It must be emphasized, too, that dysentery, largely an infection of the colon, may be due to other microbes. Any infection caused by members of the genus *Shigella* may be classified as Shigellosis. The following pages are devoted to a discussion of *Shigellae* and various aspects of Shigellosis, including diagnosis, prophylaxis and therapy.

Since Shiga's classical description of the dysentery bacillus, a number of related organisms have been found as cause of dysentery in man and have been classified within a single genus. During the first few decades following Shiga's discovery, Flexner, Duval, Sonne, Castellani, and Schmitz encountered other members of the genus. Continued research into the etiology of bacillary dysentery during recent years has brought to light the existence of a fairly large number of other microorganisms which differ in certain characteristics from the classical types of dysentery bacilli. Some of these microbes have been definitely proven to belong to the genus *Shigella*, whereas the taxonomic position of other microorganisms, tentatively described as *Shigella*, has not yet been fully elucidated. Still other bacteria, referred to in the literature as dysentery bacilli, have been shown since to belong to other genera and, therefore, have to be removed from the group of true dysentery bacilli. Indubitably, microorganisms will be encountered in the future which have the characteristics of dysentery bacilli and will be included in the genus. It is evident, therefore, that the renewed interest in this group of bacteria has brought about significant changes and that a discussion at the present time of *Shigellae* and Shigellosis is confronted with numerous difficulties and, by necessity, must be subject to revision in the future.

HISTORICAL OUTLINE

Dysentery has affected man for many centuries. It has occurred in epidemic and endemic forms and has been a very significant cause of death. It has occurred in times of peace and war. It has influenced the outcome of battles and thus influenced the history of many nations. The cause of the disease, however, remained obscure until, in 1875, Lösch published his observations on *Endamoeba histolytica* as a cause of this malady. His studies and the subsequent investigations by others established beyond doubt

the fact that a certain form of dysentery is due to an infection with this protozoon (amoebic dysentery). In the ensuing years it became evident, however, that there existed cases of dysentery due to other causes. It is not necessary to discuss here the numerous reports on the etiology of dysentery. Suffice it to mention that prior to 1898 a number of studies were carried out by Chantemesse, Vidal, Klebs, Ogata, and others. Indeed, it is quite possible that some of these observers were actually dealing with dysentery bacilli. In 1898, during a severe outbreak of dysentery, Shiga isolated from these patients a bacillus which was specifically agglutinated by the serum of convalescents. It is noteworthy that he also succeeded in isolating this microbe from the mesenteric lymph nodes. Shiga's report proved to be the most important single impetus for further investigations into the etiology and pathogenesis of bacillary dysentery. In recognition of this important contribution, this bacillus bears his name (Shiga bacillus) and related microorganisms are now grouped together as members of the genus *Shigella*.

Shortly after Shiga's publication, microbiologists in various parts of the civilized world attempted to verify Shiga's findings and thus gathered important additional data. Dysentery bacilli were isolated in the Philippines, in the United States, in Germany, and in Puerto Rico by Kruse, Drigalski, and Flexner. It was shown by Martini and Lentz that some of these microbes differed in important characteristics from the Shiga bacillus. Differences were noted in biochemical activities and antigenic structure. Moreover, Rosenthal showed that the original Shiga bacillus produced an exotoxin in contradistinction to the other dysentery bacilli.

In 1904, Duval described another member of the group. A similar or identical organism was studied by Kruse in 1907. Castellani reported on two types of lactose fermenting dysentery bacilli. In 1915, Sonne published his observations on a lactose-fermenting dysentery bacillus and gave convincing proof that this microbe, now referred to as the Sonne or Duval-Sonne dysentery bacillus, must be considered as a cause of bacillary dysentery.

Still other members of the genus *Shigella* were discovered during the ensuing years. In 1917, Schmitz isolated from patients with the clinical signs of dysentery a bacillus which closely resembles the Shiga bacillus and yet differs from this microorganism in important characteristics. A similar (or possibly identical) bacillus was described in 1918 by Andrewes as *Bacillus ambiguus*. In the same publication, Andrewes described as *Bacillus dispar* a microorganism which is identical with either *Bacillus madampensis* or *Bacillus ceylonensis* of Castellani.

In 1929, another type of dysentery bacillus was discovered by Clayton and Warren. This microorganism is now referred to as the Newcastle or Clayton-Warren bacillus. During the last decade additional members of the genus *Shigella* were described, particularly by Boyd and Sachs. It is evident, therefore, that research into the etiology of bacillary dysentery carried out during the past fifty years has shown that this malady may be caused by a relatively large number of different species and types of microorganisms belonging to a single group, the genus *Shigella*.

From University of Buffalo School of Medicine and Children's Hospital, Buffalo, New York.

THE GENUS *SHIGELLA*

The genus *Shigella* (abbreviated *S.*) is comprised of a fairly large number of species and types of microorganisms which have the following characteristics in common: They are Gram-negative, non-acid-fast bacilli; they do not form spores and do not possess capsules. The morphology of the various members offers no means of differentiation either from each other or from other non-motile, non-encapsulated, Gram-negative bacilli of the tribe *Salmonellae*. The recognized types, with the exception of *S. sp.* (Newcastle type), are generally considered to be non-motile, i. e. devoid of flagella. However, it should be pointed out that Stuart and associates (163) succeeded in inducing motility and sometimes even swarming by serial transfers in tubed semisolid agar (0.25%). This observation may necessitate revision of the definition of the genus *Shigella*. From a practical point of view, however, it is unlikely that serious difficulties will arise in the identification of strains freshly isolated from patients.

The members of the genus grow without difficulty on the usual culture media (including Endo agar) and can be maintained thereon for indefinite periods of time. They are aerobic, but may thrive also under anaerobic conditions.

With respect to biochemical activities, the recognized members of the group produce acid (an exceptional type also gas) from glucose, cause acid formation in litmus milk, form NH_3 , are Voges-Proskauer-negative, do not grow on Koser's citrate medium, do not liquefy gelatin and do not ferment urea. Most strains fail to produce H_2S , although certain Flexner and *S. alkalescens* strains do so.

Dissociation has been observed in various members of the genus. The resulting variant may differ in biochemical activity from the parent. For example, the Sonne bacillus may give rise on agar to daughter colonies, which, in contrast to the parent colony, ferment lactose. The appearance of these papillae upon prolonged incubation seems to be responsible for the late-fermentation of lactose rather than a slow utilization of this carbohydrate. Similar observations have been made by Assis (6) and by Neter and Deuchler (122) on *S. alkalescens*.

Antigenically, the various members of the genus contain species- or type-specific antigens. It is important to point out that these antigens may be comprised of different antigenic fractions and that some of the antigenic components may be shared with other types or species of the genus and even with unrelated bacteria, particularly *Enterobacteriaceae*. So far as we know, the members of the genus do not possess a common genus-specific antigen. Therefore, a monovalent diagnostic serum for the identification of unknown strains of *Shigellae* can not be procured.

Attention may be called to the fact that dissociation may result in changes of antigenic structure. Arkwright (4) has described in detail the S and R forms of *S. dysenteriae* (Shiga). The former colonies are

smooth, round and domed and the latter flattened with irregular margins and surfaces. The smooth colonies emulsify without auto-agglutination in physiological salt solution, whereas the rough colonies show clumping. In addition to these smooth and rough colonies, intermediate colonies (Rs, RS, rS forms) are frequently observed. Certain members of the genus have been shown to give rise to minute forms (dwarf or D colonies, G colonies of Hadley and G-like forms, Zwergkolonien).

The nutrient requirements of *Shigellae* have not been entirely elucidated. Reference may be made to the important studies of Koser and his associates (95, 35), who demonstrated that many Flexner and Sonne dysentery bacilli either failed to grow or grew only poorly in a basic medium consisting of 15 amino acids, glucose and inorganic salts. Addition of nicotinamide or nictinic acid exerted a marked growth-promoting effect. These substances, therefore, may be considered as essential growth factors for these strains. Individual strains vary greatly in the requirement of nicotinic acid and some strains or variants of others are able to produce this growth factor, according to Weil and Black (178). These authors found, furthermore, that certain Flexner strains require pantothenic acid.

In the past, the genus *Shigella* was subdivided into groups according to the action of the organisms upon mannitol and lactose. It has been shown that this classification, based on biochemical activities, does not entirely agree with the classification based upon antigenic structure; however, it still serves a useful purpose. It can not be emphasized too strongly that the identification as well as the classification of any strain should not be based on a single characteristic; rather that all important cultural, biochemical, and antigenic properties should be adequately considered.

A tentative subdivision of the genus *Shigella* yields the following groups:

- (1) The mannitol-negative, lactose-negative *Shigella* group.
 - (a) *S. dysenteriae* (Shiga)
 - (b) *S. schmitzii*
 - (c) *S. sp.* (Newcastle type)
 - (d) *S. sp.* (Sachs types)
 - (e) *S. sp.* (Whitcler and Stuart types)

Organisms whose inclusion in the genus has been disputed are the MacLennan and Wakefield bacilli.
- (2) The mannitol-positive, lactose-negative *Shigella* group.
 - (a) *S. paradysenteriae* (Flexner types)
 - (b) *S. paradysenteriae* (Boyd types)
 - (c) *S. sp.* (Lavington type)
 - (d) *S. alkalescens*
- (3) The mannitol-positive, lactose-positive *Shigella* group.
 - (a) *S. sonnei*
 - (b) *S. dispar*
- (4) Miscellaneous organisms.

TABLE I
Biochemical Reactions of Mannitol-Negative *Shigella*
Strains

(after Wheeler and Stuart 188)

Negative as to mannitol, salicin, adonitol, sucrose, lactose, citrate, Voges-Proskauer, and urea.

Culture	Glucose	Maltose	Rhamnose	Arabinose	Dulcitol	Xylose	Sorbitol	Indole
<i>Shigella dysenteriae</i>	A	—	—	—	—	—	—	—
sp. Sachs Q771								
arabinotarda A								
sp. Gober 8524	A	A°	—	AA°	—	—	AA°	—
sp. Sachs Q1167								
arabinotarda B	A	AA°	—	AA°	—	—	A-	—
sp. Sachs Q454	A	—	—	A	—	—	—	—
sp. Sachs Q1020	A	A°	—	A	A°	—	A°	—
ambigua	A	A°	A	A°	—	—	A°	+
sp. Sachs Q902	A	A°	A	A	—	—	—	+
sp. Wheeler and Stuart 1831	A	A°	A	A	—	A	—	+

A — acid within 24 hours; A° — acid 24 hours to 28 days;
— — no fermentation.

A discussion of these species and types follows.

SHIGELLA DYSENTERIAE (Shiga)

The cultural characteristics of the Shiga bacillus may be briefly described: Upon incubation for 24 hours on plain agar or MacConkey agar colonies in the S phase are round, shiny, smooth, sharply defined, domed and translucent. Colonies in the R phase may be either flat and thin with regular outlines and rough surfaces, or they may be moderately thick, but flattened with indented or slightly jagged margins. Generally, after 24 hours of incubation, the R forms of Shiga's bacillus are somewhat larger than the S forms. In addition to typically smooth and rough colonies, intermediate forms are frequently seen. R variants may develop from S strains spontaneously, particularly in old cultures, or under a variety of different conditions, for instance, in the presence of bacteriophage. Arkwright (4) whose investigations of the different cultural forms of the Shiga dysentery bacillus are of outstanding importance, found that changes of the cultural phase are associated with changes of other attributes as well. The S forms give stable suspensions in physiological salt solution and cause uniform turbidity in broth cultures. In contrast, the R forms agglutinate spontaneously in physiological salt solution and form a deposit in broth cultures. The reason for this different behaviour of S and R forms of *S. dysenteriae* is of interest. White (190) found that agglutination of the R form of Shiga's bacillus in physiological salt solution can be prevented, if the alcohol-soluble substances of the bacilli are previously removed.

In addition to these normal-sized colonies, cultures of Shiga's bacillus may occasionally show very small colonies, the so-called G or G-like colonies. There cannot be any doubt about the existence of this colony form. On the other hand, it remains to be seen whether or not elements of these colonies are filtrable.

The biochemical activities are summarized in Table I. It may be noted that the enzyme pattern of this organism is quite characteristic and aids greatly in the identification of unknown strains.

Wheeler and Stuart (188) reported recently that some strains of the Shiga bacillus, particularly certain old stock culture strains, may produce a weak acid reaction in lactose broth containing bromcresol purple after incubation from 14 to 28 days. In all likelihood, this late and weak acid formation does not cause serious difficulties in the identification of freshly isolated strains.

Antigenically, the R and S forms of the Shiga dysentery bacillus are distinct. This was shown by Arkwright (4) as early as 1921. Failure to correlate bacterial dissociation and accompanying changes in the antigenic structure of the Shiga bacillus accounts for many reports in the literature on so-called inagglutinable strains. Arkwright showed that rabbits immunized with pure phases of either R or S forms develop agglutinins against the homologous organisms; these antisera give only very little cross-reaction with the heterologous organism. The S and R forms of all strains are agglutinated by the respective antiserum. It is now generally agreed that in its smooth phase this

species is antigenically homogeneous. Arkwright noted, furthermore, that the S form is agglutinated in large clumps by specific antiserum, whereas the R form is agglutinated in small clumps, which are readily shaken up into a turbid suspension. Absorption experiments give further evidence of the distinct antigenic structure of these two cultural phases. Absorption of a polyvalent serum (which agglutinates both R and S forms) with the S form eliminates the antibodies to the latter without reducing to any great extent the titer of the antibodies to the R form; and vice versa, the R form absorbs its own agglutinins from such a serum without markedly reducing the titer of the antibodies to the S form. The antigen in smooth strains of the Shiga bacillus, which gives them their species-specificity, has been isolated and purified (108, 109, 130). This antigen consists of three main components: (a) a polysaccharide, (b) a polypeptide-like substance, and (c) a phospholipin. The latter seems to be of minor significance. The polysaccharide is a typical hapten; alone it does not induce the formation of antibodies *in vivo*. The polysaccharide-polypeptide mixture engenders antibodies against both components. It is interesting to note that antibodies against the polypeptide are not present in immune sera prepared by the injection of the organisms themselves. The significance of these antibodies in immunity remains to be elucidated.

In addition to the species-specific bacterial polysaccharide, the Shiga bacillus may contain other antigenic components, for instance, antigens in common with human blood cells (42, 43, 149). The significance of the Forssman and blood-group antigens in Shiga's bacillus and, particularly, their relationship to pathogenicity, remain to be determined. The chemical structure of the antigen or antigens characteristic of the R phase of the Shiga dysentery bacillus is not known as yet.

A few years following the discovery of the Shiga dysentery bacillus, it was found that sterile culture filtrates were toxic for rabbits, causing diarrhea, paralysis of the extremities (due to lesions in the central nervous system) and death. The exotoxin of *S. dysenteriae* is often referred to as a neurotoxin, because it affects the nervous system. It is highly reactive in rabbits and horses and less so in mice, guinea pigs, and rats. It may be obtained by filtration of broth cultures; incubation of two weeks yields smaller amounts of exotoxin than incubation for three to four weeks. The exotoxin may also be procured from the bacterial cells themselves, for instance, by repeated freezing and thawing, by shaking, by chemical methods and also by the action of bacteriophage.

During recent years, several attempts have been made to separate the exotoxin of the Shiga bacillus from the endotoxin. Olitsky and Kligler (126), Boivin and Mesrobian (13, 14, 15), and Haas (71) claim to have accomplished this separation. These authors report, furthermore, that the exotoxin affects the nervous system (neurotoxin), whereas the endotoxin causes lesions of the intestinal tract (enterotoxin).

Formaldehyde exerts a characteristic influence upon

the exotoxin in reducing its toxicity without diminishing its antigenic properties to any great extent. The formaldehyde-treated exotoxin (toxoid) of Shiga's bacillus is not completely devoid of toxicity (72). The toxoid may be successfully used for the immunization of animals in order to obtain high-titered antisera for therapeutic purposes. The mortality rate of the animals injected with toxoid is markedly lower than that of the animals immunized with untreated toxin. Antigens for immunization of man will be discussed later.

SHIGELLA SCHMITZII (S. AMBIGUA)

In 1917, Schmitz (151) isolated from patients with clinical signs of dysentery a bacillus which showed certain similarities to Shiga's bacillus and yet revealed striking differences. A similar microorganism was studied by Andrewes (2) in 1918, who referred to it as *Bacillus ambiguus*. It is true that Schmitz' bacillus has been recognized as a cause of bacillary dysentery and that Andrewes' bacillus was considered to bear no relationship to dysentery of man. In this connection it may be pointed out that the factors responsible for pathogenicity of certain strains, types, and species are still very incompletely known. Thus far, no evidence has been presented to show how these organisms can be differentiated from each other. Until such time, it is reasonable to consider them as a single species or type.

S. schmitzii resembles Shiga's bacillus, but it may readily be distinguished from the latter by its capacity to form indole and to produce acid from rhamnose (Table I). Antigenically, too, it is distinct from Shiga's bacillus. Antisera to the Schmitz bacillus obtained from rabbits agglutinate Shiga's bacillus only slightly or not at all. Likewise, antisera to Shiga's bacillus fail to agglutinate to high titer the bacillus of Schmitz. When cross-reactions are encountered, agglutinin-absorption tests allow a definite differentiation of the two organisms. *S. schmitzii* is antigenically homogeneous. Another important difference between the two species exists with respect to their toxicity, the Shiga bacillus producing a powerful exotoxin, while *S. schmitzii* does not. The Schmitz bacillus can be differentiated from the Sachs types by means of type-specific antisera.

SHIGELLA SPECIES (NEWCASTLE TYPE)

In 1929, Clayton and Warren (25, 26) isolated from patients presenting symptoms of dysentery a microorganism, which they considered to be the cause of the malady and which differed from previously described species. Since then, this species has been encountered also in the United States and in other parts of the world.

S. sp. (Newcastle type) is considered to be motile. It produces acid and gas from glucose, maltose, and dulcitol; it fails to attack lactose, sucrose, and mannitol; it causes acid-formation in litmus milk and does not produce indole. Strains similar to the Newcastle bacillus, but which ferment mannitol, have been described (36) (Manchester type).

Antigenically, these two biotypes are identical and share the type-specific antigen with a member of the

TABLE II
Biochemical Reactions of Type 88, Manchester Bacillus,
and Newcastle Bacillus
(after Boyd 18)

	Lactose	Glucose	Mannitol	Dulcitol	Sucrose	Indole
Type 88 (33% of strains)	—	Acid	Acid	—	—	—
Type 88 (66% of strains)	—	Acid	Acid	Acid (late)	—	—
Manchester bacillus	—	Acid and gas	Acid and gas	Acid and gas (late)	—	—
Newcastle bacillus	—	Acid and gas	—	Acid and gas (late)	—	—

Flexner group (type 88). Therefore, the three biotypes (Newcastle, Manchester, and 88) are now considered as members of a single serotype of the Flexner-Boyd group of dysentery bacilli (see page 219). It is interesting to note that the Newcastle bacillus bears no antigenic relationship to the Shiga bacillus. It may be mentioned in this connection that patients with dysentery due to *S. sp.* (Newcastle type) may develop specific agglutinins.

THE SACHS TYPES

In 1943, Sachs (144) published his studies on eight serological types of mannitol-negative *Shigella* organisms which differed from the recognized species of the group, *S. dysenteriae* (Shiga), *S. schmitzii*, and *S. sp.* (Newcastle type). Four of these eight types had been previously described by Large (97) and by Large and Sankaran (98). Members of the mannitol-negative *Shigella* group have been described also by Christensen and Gowen (24) as *S. arabinotarda* types A and B, by Gober, Stacy, and Woodrow (65) as "No. 8524" and by Berger (10) as *Bacterium wakefield*.

A reinvestigation of the mannitol-negative *Shigella* group was competently carried out by Wheeler and Stuart (188), who obtained the following results:

- (1) Sachs type Q771, *S. arabinotarda* type A of Christensen and Gowen and "No. 8524" of Gober are serologically identical.
- (2) Sachs type Q1167 and *S. arabinotarda* type B of Christensen and Gowen are serologically identical and distinct from the others.
- (3) Three types (A12, B81, B105), described by Sachs, do not belong to the genus *Shigella*, since these organisms are motile or produce gas. Likewise B. wakefield of Berger should be eliminated from the genus *Shigella*, because it is motile; it is a member of the paracolon bacillus group. It may be added that a non-mannitol fermenting dysentery bacillus (P25) described by MacLennan in 1945 should not be considered as a member of the *Shigella* group since, according to Wheeler (personal communication), it has become motile.

Keeping in mind that motility has been observed

with the prototype of dysentery bacilli, namely, *Shigella dysenteriae* (Shiga), and also with the Newcastle bacillus, final judgment regarding the taxonomic position of the organisms just mentioned should be deferred in the opinion of the present writer.

Evidence has been presented by Sachs and other investigators that the Sachs types may be pathogenic to man. These strains have been isolated from patients suffering from dysentery living in India and Egypt. It is also worthy of note that patients harboring these microorganisms may develop antibodies in titer above normal.

SHIGELLA SPECIES (WHEELER AND STUART TYPE)

Wheeler and Stuart (188) very recently described a new serotype of a mannitol-negative dysentery bacillus. Further investigations are necessary before its significance can be appraised.

THE MACLENNAN BACILLUS

As just mentioned, the MacLennan may have to be removed from the genus *Shigella*. It has been found by Wheeler (personal communication) to be motile. It produces acid from glucose and sucrose and does not form acid from mannitol, lactose, dulcitol, and rhamnose. It produces indole. It differs serologically from other non-mannitol-fermenting dysentery bacilli.

THE WAKEFIELD BACILLUS

In 1945, Berger (10) isolated from patients suffering from diarrheal disease a microorganism which has been considered as a new member of the genus *Shigella*. Since this microbe was first found in Wakefield, England, it was given the name of Wakefield bacillus.

According to Wheeler and Stuart (188) this organism should be eliminated from the genus *Shigella*. The organism forms acid from glucose, but not from lactose, mannitol, maltose, dulcitol, rhamnose, arabinose, or salicin. Two of the strains did not form indole and a third strain occasionally produced small amounts. Weil, Binder, and Slafkovsky (176) observed that this bacillus differs from the other mannitol-

negative *Shigellae* in antigenic structure. These authors also found that two antigenic types of this bacillus exist (types A and B), which share a heat-labile antigen, but differ in the heat-stable antigen. The heat-labile antigen is shared with Sachs type Q454.

SHIGELLA PARADYSENTERIAE

SHIGELLA SP. (FLEXNER-BOYD TYPES)

AND

SHIGELLA ALKALESCENS

S. paradyenteriae is comprised of biochemically and antigenically different types of microorganisms. In the past, great emphasis was placed on biochemical differences of these strains and, on that basis, Flexner, Hiss-Y-Russell and Strong types were recognized. This classification has been completely abandoned in favor of that largely based on antigenic structure. The group, then, comprises a fairly large number of serotypes, including the Flexner group of bacilli of the older literature and the more recently discovered types of Boyd. Thus, we may conveniently speak of the Flexner-Boyd group of dysentery bacilli.

The biochemical characteristics of the group may be briefly summarized as follows: The organisms produce acid from glucose; one particular type (type VI) produces acid and gas. Most types ferment mannitol with the formation of acid; the Newcastle bacillus, belonging to type VI, does not acidify this substrate. As shown by MacLennan (105), certain types of the group may give rise to variants which, in contradistinction to the parent strain, fail to ferment mannitol. The members of the group do not produce acid from lactose. The majority of strains give a negative Eijkman test and fail to reduce trimethylamine oxide (Wood test). Some strains form H_2S (Frierer and Shaughnessy 60). Otherwise, the organisms have the characteristics of all *Shigellae*.

The British investigators Andrewes and Inman (3) studied the Flexner group in detail and described five serotypes, referred to as *S. paradyenteriae* V, W, X, Y, and Z. A re-investigation of singular importance was carried out by Boyd (18). He found that approximately 75% of his strains corresponded to the types described by Andrewes and Inman. The remaining 25% included nine additional types. Weil, Black, and Farsetta (179) studied the antigenic pattern of the various types included in the Flexner-Boyd group. They identified fourteen primary antigens. Correspondingly, there were found fourteen antigenic types, each containing one of these primary antigens. These authors recognized two additional types, each harboring two different primary antigens. The primary antigens are of great importance; unknown strains can be identified by demonstrating these antigens and an understanding of the antigenic pattern aids in attempts of active immunization and serum therapy. It should be emphasized, however, that members of the Flexner-Boyd group may contain additional antigenic components. This is well illustrated by the type P274 one antigen of which is specific for this particular type, another is shared with certain paracolon bacilli,

and still another is found also in *S. alkalescens*. Moreover, individual strains exhibit minor antigenic differences. In all likelihood, similar conditions prevail regarding the other types.

In 1946, Heller and Wilson (87) published studies on a microorganism referred to as *S. etousae*. The organism has the characteristics of the *Shigella* group. It produces acid (but no gas) from glucose, galactose, mannitol, xylose, sorbitol, and arabinose. Maltose, dextrin and glycerol are fermented after 7 to 14 days. No acid is produced from lactose, sucrose, salicin, dulcitol, rhamnose, inulin, starch or inositol during 21 days' incubation. Litmus milk becomes acid 24 hours after inoculation. The Eijkman test is negative. All strains readily form indole and reduce tetramethylamine oxide to trimethylamine. These strains represent an antigenically distinct type.

Ewing (44) described the characteristics of *Shigella* strains which he considered to represent a new serotype. The organism has been referred to as *S. paradyenteriae* (Lavington I). In all probability, *S. etousae* and *S. paradyenteriae* (Lavington I) are identical.

Little doubt exists regarding the pathogenicity of the Flexner-Boyd group of dysentery bacilli. Lavington, Matheson, Taylor, and Fleming (99) presented evidence to the effect that *S. etousae*, too, is pathogenic to man, causing bacillary dysentery. In passing, it may be mentioned that the serum of 18 out of 20 patients studied contained type-specific antibodies.

In 1946 two additional serotypes of the Flexner group were described by Francis (59), who named them provisionally Flexner types VI and VII, respectively. Before summarizing the present-day status of the mannitol-positive, lactose-negative group of dysentery bacilli and before presenting the classification of the sero-types included in the group, it seems feasible to discuss first *S. alkalescens*, an organism which closely resembles the Flexner-Boyd group and ultimately may even be classified as one of its members.

S. alkalescens was first described by Andrewes (2) in 1918. The biochemical activities are quite characteristic. It produces acid (but not gas) from glucose, maltose, mannitol, rhamnose, xylose, and dulcitol. Sucrose is occasionally fermented. As a rule, acid is not produced from lactose. In litmus milk, following a transitory acidification, it produces a characteristic strong alkaline reaction. Indole is formed. Trimethylamine oxide is reduced to trimethylamine. Most strains give a positive Eijkman reaction. Some strains produce H_2S (Galton and Hess 63).

S. alkalescens may give rise to variants which differ in biochemical activities from the parent strain. Neter and Deuchler (122), for example, observed a strain which fermented rhamnose readily and which gave rise to variants which failed to do so. Assis (6) observed lactose-fermenting variants.

Antigenically, most strains contain a species- or type-specific antigen. Stuart, Rustigian, Zimmerman, and Corrigan (162) investigated the antigenic struc-

TABLE III
Shigella (S.) Paradysenteriae
(Flexner-Boyd group)

Andrewes and Inman	Boyd	Weil et al.	Neter
			A. Flexner group
1. V	Flexner I	S. paradysenteriae type I	S. sp. (Flexner type I)
2. W	Flexner II	S. paradysenteriae type II	S. sp. (Flexner type II)
3. Z	Flexner III	S. paradysenteriae type III	S. sp. (Flexner type III)
4.	Flexner IV (type 103)	S. paradysenteriae type IV	S. sp. (Flexner type IV)
5.	Flexner V (type P119)	S. paradysenteriae type V	S. sp. (Flexner type V)
6.	Flexner VI (88-Newcastle group)	S. paradysenteriae type VI	S. sp. (88-Newcastle group)
7.	Flexner VII (see Francis)		S. sp. (Flexner type VII)
8.	Flexner VIII (see Francis)		S. sp. (Flexner type VIII)
9. X		S. paradysenteriae type VII	S. sp. (Flexner type IX)
10. Y		S. paradysenteriae type VIII	S. sp. (Flexner type X)
11. VZ		S. paradysenteriae (type I, III)	S. sp. (Flexner type I, III)
12. WX		S. paradysenteriae (type II, VII)	S. sp. (Flexner type II, IX)
			B. Boyd group
13.	Boyd I (type 170)	S. paradysenteriae (type IX)	S. sp. (Boyd I)
14.	Boyd II (type P288)	S. paradysenteriae (type X)	S. sp. (Boyd II)
15.	Boyd III (type D1)	S. paradysenteriae (type XI)	S. sp. (Boyd III)
16.	Boyd IV (type P274)	S. paradysenteriae (type XIV)	S. sp. (Boyd IV)
17.	Boyd V (type P143)	S. paradysenteriae (type XIII)	S. sp. (Boyd V)
18.	Boyd VI (type D10)	S. paradysenteriae (type XII)	S. sp. (Boyd VI)
			C. Other types
19.		S. lavington (S. etousae)	S. sp. Lavington type (S. etousae)
20. S. alkalescens			S. alkalescens (Andrewes)

ture in great detail and found that three subtypes exist. All strains contain the antigens A, B, C; the three subtypes contain the antigens D and E, either singly or in combination. These strains have been referred to also as *S. alkalescens* type I. In addition to their own type-specific antigenic complex, they may share antigenic components with *S. paradysenteriae* (Flexner-Boyd group).

S. alkalescens can be differentiated from the Flexner-Boyd types on the basis of biochemical reactions and antigenic structure. No single test by itself is entirely reliable. In contrast to *S. paradysenteriae*, *S. alkalescens* usually produces acid from rhamnose, dulcitol, and xylose; gives positive Wood and Eijkman reactions, and contains its own species- or type-specific antigen.

Assis (5) described *S. alkalescens* type II, which produces acid from salicin and fails to ferment dulcitol and rhamnose. Antigenically, it is distinct from *S. alkalescens* type I. It, too, may give rise to biochemical variants. Its taxonomic position remains to be determined.

Two other strains have been described as *S. alkalescens* types III and IV, because they are identical in cultural and biochemical characteristics with *S. alkalescens* type I and differ from type I and each other in antigenic structure (Neter 119). One of these types is considered by other investigators to be Flexner type VII and *S. dispar*, respectively (Francis 59, Carpenter, and Stuart 22). The taxonomic position of these organisms, therefore, requires reconsideration.

S. alkalescens may be found in the intestinal tract of man free of enteric disease (Synder and Hanner 158). Recent reports indicate that *S. alkalescens* may cause mild and even severe forms of dysentery or enteritis. For this reason and because of its close similarity to *S. alkalescens* type I may be included in the Flexner-Boyd group of dysentery bacilli.

S. alkalescens may infect organs other than the gastro-intestinal tract; it causes cystitis, pyelitis, and septicemia. Patients suffering from *S. alkalescens* infection may develop specific agglutinins.

It is obvious that a final and generally acceptable classification of the Flexner-Boyd group of dysentery bacilli can not be presented at the present time. An attempt at taxonomy is made extraordinarily difficult in view of the multiplicity of names given to individual types. Moreover, future research may necessitate changes. Therefore, any system presented at this time should make proper allowance for required revisions. It also should be kept in mind that generally-accepted terms, even if not entirely correct, may have to be retained. The classification proposed by the present writer has been evolved on the basis of these considerations. The above table, then, presents a summary of classifications according to Andrewes and Inman, Boyd, Weil, and associates, and Neter.

SHIGELLA SONNEI

Late-lactose-fermenting members of the genus *Shigella* were described as early as 1904 by the American Duval and 1907 by Kruse in Germany. Later Castel-

lani published his studies on this group of organisms. In 1915, Sonne (159) reported his extensive and thorough investigations and established beyond doubt the fact that this organism causes dysentery in man. Because several authors were accredited with the discovery of this organism, it was given a number of names, such as Duval bacillus, Duval-Sonne bacillus, Kruse-Sonne bacillus, Kruse-E bacillus, and *B. ceylonensis* A.

The Sonne dysentery bacillus grows well on ordinary media, often somewhat more luxuriantly than either the Shiga or the Flexner dysentery bacillus. Mention should be made of the fact that phase II of *S. sonnei*, to be discussed later, may be inhibited on the selective culture media (SS and desoxycholate agar). Upon isolation on lactose-containing culture media, this organism first gives rise to non-lactose-fermenting colonies. Upon prolonged incubation, however, the size of the colonies increases and papillae or daughter colonies appear. These papillae consist of raised, smooth, entire, rounded outgrowths on the surface. They ferment lactose. A few strains fail to develop these papillae, even upon incubation for two months. Late-fermentation of lactose (and also of sucrose) occurs following the appearance of these rapidly lactose-fermenting daughter colonies.

Recently Wheeler and Mickle (187) reported on their extensive investigations into the various colony forms of *S. sonnei*. Phase I colony on tryptose agar after 24 hours incubation are circular, 2-3 mm. in diameter, convex, often with a raised center, smooth, glistening, entire, translucent, butyrous and easily emulsifiable. This phase I colony may give rise to offspring having the characteristics of phase I or phase II. The phase II colony has the following characteristics: "circular, about 5 mm. in diameter, conical or low convex, generally slightly umbonate, amorphous to finely granular, smooth to beaten copper surface, glistening, undulate margin, translucent edge with denser center, butyrous but sometimes showing slight granularity when tested with the needle and easily emulsifiable." This type breeds true. Both I and II phases give turbid growth in nutrient broth and are not flocculated by physiological saline solution. In addition to these phases, *S. sonnei* exist also as a rough type. After 24 hours on tryptose agar, rough colonies are "8-10 mm. in diameter, flat, diffuse, with slight umba, granular, dull surface, undulate to lobate margins, opaque, friable, and not emulsifiable." This type breeds true. It grows in broth with a granular sediment and will not produce a smooth suspension in saline except after prolonged shaking.

In addition to normal-sized colonies, *S. sonnei* may give rise to G-like colonies, which have a diameter of only 0.012 to 0.2 mm. It should be emphasized, however, that these dwarf colonies are observed only infrequently. Chinn (23) reported that these colonies represent approximately 1% of all colonies of old strains. It may be mentioned also that these dwarf colonies are much less active biochemically than the normal-sized colonies. Some, but not all, G-type col-

onies revert to normal-sized colonies upon prolonged incubation on agar or following repeated serial transfers to broth or agar. As far as the present writer is aware, G-colonies of *S. sonnei* have not been recovered directly from lesions in man.

Biochemically, *S. sonnei* produces acid without gas from glucose, lactose, sucrose, mannitol, maltose, and rhamnose. Lactose- and sucrose-fermentation may not become evident until a lapse of days or even of several weeks. Xylose and dulcitol are not fermented. Indole is not formed. Litmus milk becomes acid and may clot.

Until recently, the Sonne dysentery bacillus was considered to represent an antigenically homogeneous species. Glynn and Starkey (64) have studied the antigenic structure of two types of Sonne dysentery bacilli in detail. More recently Wheeler and Mickle (187) found that the three cultural types observed on agar differ also in antigenic structure. It is important, therefore, to have available for diagnostic purposes a serum containing antibodies against the antigens of phase I and phase II, as well as of the rough type. The antigen of phase II is complex. Some of the components are shared by other *Enterobacteriaceae*, for example, by *S. paradysenteriae*. Mention may be made that so-called inagglutinable strains may be specifically agglutinated by Sonne serum, if the test is carried out at temperatures ranging from 45° C. to 55° C. instead of 37° C. or if the mixture of serum and suspension is centrifuged. By means of the determination of the susceptibility of strains of *S. sonnei* to seven bacteriophages of different origin, Hammarström (75) identified fourteen different types. This method may conceivably be used with success in epidemiological studies. The relationship of these phage-types to the recognized sero-types remains to be elucidated.

SHIGELLA DISPAR

(*S. Ceylonensis* B. *S. Madampensis*, and Related Organisms)

Castellani, in 1907 and 1911, described two types of mannitol-positive, lactose-positive *Shigella* under the name of *B. ceylonensis* B. and *B. madampensis*. The former microorganism was isolated from the feces of patients with clinical signs of dysentery and the latter from individuals suffering from colitis and cystitis. In 1918, Andrewes (2) described a group of similar or identical organisms under the name of *Bacillus dispar*. So far as the nomenclature of this group of microorganisms is concerned, agreement should be reached among microbiologists as to whether this group should be named *S. dispar* or *S. castellanii* or whether it should be subdivided into *S. ceylonensis* B and *S. madampensis*, respectively.

Colonies of *S. dispar* on agar resemble those of the Sonne bacillus. They, too, may show secondary papillae. *S. dispar* produces acid from glucose, lactose, sucrose, mannitol, maltose, rhamnose, and xylose. It should be noted that acid-formation from lactose and sucrose may become evident only after incubation of one to

two weeks. Dulcitol is not fermented by *S. madampensis*, whereas *S. ceylonensis* B may produce acid from this substrate. Ewing (personal communication) recently studied several strains of *S. dispar* and found three biotypes, differing in their action upon sucrose, dulcitol, rhamnose, and xylose. *S. dispar* causes acid-formation and clotting in litmus milk. Indole is produced. Indole production distinctly differentiates *S. dispar* from the Sonne bacillus. According to Forsyth (57), *S. dispar* is methyl red positive, whereas *S. sonnei* is not. *S. dispar* reduces trimethylamine oxide.

Glynn and Starkey (64), as well as Forsyth (57) reported that *S. dispar* is heterogeneous antigenically. Recent studies by Carpenter (21) have established four distinct serotypes and several subtypes. It is interesting to note that no direct relationship exists between biochemical activities and antigenic structure. For this reason, Carpenter believes that the biotypes *S. madampensis* and *S. ceylonensis* B should not be recognized.

That *S. dispar* strains may share antigenic components with other *Shigellae* has been reported by Watanabe (171) as well as by Welch and Mickle (182). According to Carpenter and Stuart (22), *S. dispar* type II shares antigenic components with Boyd's type V (type P143) of the *S. paradysenteriae* group. It may be noted in passing that Ewing's strain No. 2193, which has been classified as Boyd type V, Flexner type VII, *S. alkalescens*, and *S. dispar* has the antigenic pattern of *S. dispar* type II-b, according to Carpenter and Stuart, although, as agreed upon by all investigators, its biochemical reactions are those of *S. alkalescens*. Finally, it may be mentioned that strains of *S. dispar* share antigenic components with aerogenic *Enterobacteriaceae* (Ewing, personal communication).

S. dispar has been isolated from feces of healthy individuals as well as from patients with intestinal disease. Johnston and Kaake (92) reported several cases of enteritis in children from whom this microbe was isolated. Boyd recently recovered this microorganism from clinical cases of dysentery. Further investigations are needed and particular attention should be paid to the question as to whether or not this species may be responsible for epidemic outbreaks of dysentery.

MISCELLANEOUS BACTERIA

In the past, a number of additional organisms were included in the genus *Shigella*. Some of these microbes have been described only inadequately and, apparently, have not been dealt with in recent years. Unless further information on these strains becomes available, it is impossible to include them in this particular genus. Other organisms, previously considered to be dysentery bacilli, have now been shown to belong to other genera. *S. septicemiae* and *S. minutissima* were considered as mannitol-negative, lactose-negative dysentery bacilli. *B. rettgeri* and *B. pfaefli*, formerly included in the genus *Shigella* as mannitol-positive, lactose-negative members, are probably motile and should be eliminated from the genus. *B. gallinarum* should be considered as an anaerogenic *Salmonella* organism, specifically as *Salmonella gallinarum*. *B. hienstoekli* and *B. oxygenes*, supposedly lactose-positive, mannitol-negative *Shigellae*, have been investigated only very inadequately and the reports on their characteristics are conflicting. Finally, reference may be made to *B. equirullis*,

which differs from the recognized *Shigellae*, inasmuch as it is responsible for disease of young foals (arthritis, nephritis, and septicemia). So far as the present writer is aware, this microorganism is not a cause of bacillary dysentery in man. For further data on these species, the reader is referred to Bergey's Manual (11) and Neter's (117) review on the genus *Shigella*.

SHIGELLA INFECTIONS IN ANIMALS

It has been pointed out previously that Shigellosis is essentially a disease of man. Only on rare occasions has spontaneous illness caused by these microorganisms been observed in monkeys and dogs. An interesting study was reported by Janota and Daek (91), who found that captive *Macaca mulatta* may be carriers of Flexner dysentery bacilli and that dysentery may develop in these animals on diet deficient in vitamin M.

Experimental dysentery can be produced with dysentery bacilli. Dack and Hoskins (33), for example, induced this disease in isolated loops of the colon of *Macaca mulatta*.

Dysentery bacilli may also cause infections other than dysentery in experimental animals. Injection into rabbits of living cultures of *S. dysenteriae* (Shiga) or its toxin produces haemorrhagic enteritis; a pseudo-membranous exudate develops on the surface of the mucosa. The development of paralysis and corresponding changes in nerve cells of the spinal cord in some of the animals has been attributed to the action of the neurotoxin. The toxin of the Shiga bacillus is highly reactive in rabbits and horses and less so in mice, guinea-pigs, and rats. The Shiga bacillus is more toxic to rabbits than are Flexner and Sonne dysentery bacilli.

It is noteworthy that feeding of dysentery bacilli to a variety of laboratory animals is followed only rarely by the development of intestinal lesions. On the other hand, these microbes, as for example Flexner and Sonne dysentery bacilli, suspended in mucin, upon intraperitoneal injection, cause peritonitis and haeteremia in mice. Olitzki and Koeh (128) recently studied the effects of various mucin preparations. They found that, if a mucin preparation is to be effective, it should remain in the abdominal cavity for a relatively long period of time and it should absorb and destroy white blood cells. From the studies of these authors it is evident that mucin decreases the natural resistance of the host rather than increases the virulence of the organism.

Well and Gall (180) infected chick embryos with *S. paradysenteriae*. This experimental disease has been utilized for the appraisal of prophylactic and therapeutic agents.

CLINICAL ASPECTS OF SHIGELLOSIS IN MAN

Bacillary dysentery is the most important malady of man caused by members of the genus *Shigella*. It is characterized by an inflammatory lesion of the intestinal tract. In classical cases the colon, cecum, and rectum are mainly involved and lesions may also be present in the lower portion of the ileum. Only rarely is the entire small intestine affected.

The incubation period of bacillary dysentery usually is relatively short, ranging from 12 to 72 hours, but it may be as long as seven days. The malady occurs in every age group. Often it is acute; subacute and chronic cases are also observed. Relapses may be encountered. The disease may be extremely mild (subclinical infection) or it may be mild, fairly severe, severe, or fatal.

In the classical case the onset is sudden. The patient has fever and abdominal pain; diarrhea is usually present, and the bowel discharges may contain blood, mucus, or both. The number of stools varies from case to case and from day to day and may be as high as 30 to 40 in a 24-hour period. It can not be stressed too strongly that many cases of Shigellosis present a clinical picture of simple diarrhea. Such cases are frequently not properly investigated and recognized.

The fecal discharge contains mucus, leucocytes, macrophages, and red blood cells, as evidenced by microscopic examination. Increase in the number of leucocytes usually is indicative of extension of ulceration. Conversely, healing of the lesions of the intestine is followed by a decrease in the number of leucocytes and the amount of exudate; the mucus becomes thicker.

In addition to these more or less typical cases, Shigellosis may simulate other clinical syndromes. It should be emphasized that a fairly large number of these patients present the picture of a febrile disease without specific localization, particularly without the predominant feature of diarrhea. Such cases may be erroneously diagnosed as influenza. Felsen (49) has described the appendicular, meningitic, pneumonic, agranulocytoid, constipated, afebrile and asymptomatic forms of the disease. For further data on the clinical aspects of Shigellosis, the reader is referred to the books of Felsen (49) and Rockus (12).

Members of the genus *Shigella* occasionally cause diseases other than bacillary dysentery, for example, infections of the urinary tract, bacteremia, and septicemia, as well as localized purulent lesions (abscesses, empyema, etc.). It should be stressed, however, that these maladies are only rarely caused by the Shiga, Flexner, and Sonne dysentery bacilli. More often, *S. alkalescens* is the causative agent. For further data, the reader is referred to the reports of Neter and Fisher (123), Felsen and Wolarsky (50), Stewart (160), Ravenswaay (138), Neter (114), Pasricha and De Monte (131), Thompson (167), Snyder and Haner (158), and Neter and Heide (124).

INCIDENCE OF BACILLARY DYSENTERY

Bacillary dysentery is a common disease, affecting all ages and prevalent in many parts of the world, particularly in the tropics, sub-tropics, and in the moderate zones. Any attempt to determine the actual incidence of this malady is confronted with serious difficulties and, by necessity, must be largely inaccurate. It should be kept in mind that many patients suffering from a mild form of the malady do not seek medical advice and, thus, these cases are not included in statistical reports. Moreover, since bacteriological examinations frequently are not carried out, data on the incidence of Shigellosis yield figures far short of the actual occurrence of the disease. On the other hand, reliance on the clinical diagnosis exclusively leads to the inclusion of enteric diseases other than Shigellosis. In 1933 the League of Nations (100) published the most extensive report available on the incidence of dysentery in the world. Unfortunately, no differentiation is made between amoebic and bacillary dysentery in reports from many states and countries and from others statistical data are entirely lacking. With respect to the incidence of this disease in the United

States, the following figures collected by the United States Public Health Service may be presented.

Year	Incidence of Bacillary Dysentery
Median, 1938-1942	20,950
Median, 1939-1943	24,056
Median, 1940-1944	24,281
1940	19,152
1941	24,281
1942	24,056
1943	30,872
1944	37,525
1945	34,672

In Japan, in a single year (1929), bacillary dysentery caused the death of 3,166 adults and over 10,000 children.

Between August 1940 and June 1943, Boyd (20) investigated 64,972 cases of clinical dysentery encountered in Middle East forces — a striking indication of the importance of this malady.

During the last few years, much valuable information has been accumulated with respect to the incidence of different dysentery bacilli as cause of Shigellosis. Boyd (20) studied a total of 23,950 strains; 94.5% were typed serologically. The results obtained are summarized in the following table.

Percentage of various dysentery bacilli isolated

<i>S. dysenteriae</i> Shiga	18.86
<i>S. schmitzi</i>	6.68
<i>S. sonnei</i>	7.37
<i>S. paradyenteriae</i>	
Flexner I to VI and Boyd I	61.59
Other non-mannitol fermenters	2.16
Other mannitol fermenters	3.34

Among the strains submitted as atypical, the following types were encountered:

Boyd II (P288)	
Boyd III (D1)	
Boyd IV (P274)	
Boyd V (P143)	
Flexner VIII, a new dysentery bacillus of the group <i>S. dispar</i> .	

Randall and Dunn (137) isolated the following types of dysentery bacilli from military personnel in North Africa.

	Total	Cultures From Food Handlers	Per Cent
Flexner I, II, III (Andrewes and Inman series)	200	17	46.9
Flexner IV (Boyd 103)	9	2	2.1
Flexner V (Boyd P119)	4	0	0.9
Flexner VI (Boyd 88-Newcastle-Manchester group)	69	13	16.2
Boyd I (Boyd 170)	9	0	2.1
Boyd III (Boyd D1)	1	0	0.2
Boyd P274	9	1	2.1
Boyd P143	5	1	1.2
<i>S. ambigua</i>	11	0	2.6
<i>S. madampensis</i>	2	1	0.5
<i>S. ceylonensis</i>	8	7	1.9
<i>S. dysenteriae</i>	10	5	2.3
<i>S. sonnei</i>	66	3	15.5
<i>S. alkalescens</i>	5	0	1.4
Sachs Q1030	2	0	0.5
Unidentified Cultures From Food	15	0	3.5

During the years 1942 and 1943, 596 strains of *S. paradyenteriae* were isolated in Puerto Rico by Gonzalez and Otero (53). The majority of these strains belonged to types V, W, and Z, 88-Newcastle, and Boyd 103.

Assis and his associates (8) identified 200 dysentery bacilli from patients with acute and chronic dysentery in Rio de Janeiro. The distribution of the types was as follows:

Flexner W.	34.5%
Flexner Z	19.0%
Flexner V	7.5%
Flexner VZ	16.0%
Flexner Y	3.0%
Flexner X	1.0%
Flexner type VI (88-Newcastle group)	2.0%
Boyd 103	2.0%
Boyd P288	2.0%

Boyd's types D1 and P274 were found only rarely. Representatives of three other Boyd types were not encountered.

CASE FATALITY RATE IN BACILLARY DYSENTERY

At the present time, it is very difficult, if not impossible, to give reliable data pertaining to the case fatality rate in bacillary dysentery. Probably, it is lower than it appears from the literature. This is particularly so because many mild cases escape detection. The fatality rates show great variations at different times and in different locations and may range from less than 1% up to 50% and higher. The outcome in bacillary dysentery depends upon many factors, for instance, the type of infecting microorganism, localization and extent of the lesions, age and general condition of the patient, complications and concomitant diseases, therapeutic measures, and others. Shiga (156) reported rates ranging from 22% to 55% among dysentery patients treated without serum in hospitals during the period from 1895-1899. Series of patients with bacillary dysentery without fatalities, too, have been encountered. Among the 21,327 reported cases of bacillary dysentery observed in the United States during 1939 there were 1,049 deaths, a fatality rate of slightly above 5%. During the period from 1937 to 1941 6,652 cases of bacillary dysentery were reported in the State of New York; there were 145 deaths; the mortality rate amounted to slightly above 2%.

TRANSMISSION AND PATHOGENESIS OF BACILLARY DYSENTERY

Since bacillary dysentery is essentially a disease of man, the most important reservoir of dysentery bacilli are individuals suffering from shigellosis or excreting *Shigellae*. Most commonly, dysentery bacilli reach the outside world through feces. Only rarely are these organisms eliminated with the urine. Fecal contamination, either directly or indirectly, accounts for infection of other individuals and for the contamination of water, milk, food, etc. Hardy and Watt (79) isolated *Shigellae* with comparative ease from the fingers or fingernails of known cases and carriers. The significance of the lack of sanitary conditions for the spread of dysentery bacilli is well brought out by the fact that bacillary dysentery by no means rarely occurs endemically and epidemically in groups living under poor hygienic conditions and also among inmates of asylums for the insane.

The importance of the contamination of water and food cannot be underrated. Fyfe (61) observed a milk-borne outbreak of Sonne dysentery involving 150 persons. Godfrey and Pond (66) described an epidemic originating from contaminated ice; 60 cases among employees of a hospital were involved. An outbreak of the disease, due to contaminated water, was reported by Shadday (154). It occurred on the U. S. S. Salt Lake City and involved 14% of the personnel. Another outbreak of 3,000 cases due to sewage entering the water distributing system was studied by Kinninan and Beelman (93).

There can be little doubt that flies play an important role in the dissemination of dysentery bacilli. Indeed, *Shigellae* have been isolated from these vectors. Furthermore, a relationship exists between the incidence of bacillary dysentery and prevalence of flies. A large outbreak of more than 1,500 cases of bacillary dysentery in which flies played a major role in the transmission of the disease was reported recently by Kuhns and Anderson (96). It has been stated that ants may possibly carry dysentery bacilli and thus spread the infection (Griffiths 70).

In the vast majority of cases, dysentery bacilli enter the human body through the mouth. Only rarely is the rectum the portal of entry, for example, following enemas or proctoscopic examinations.

Usually, the dysentery bacilli remain localized in the intestinal tract, causing lesions, particularly in the large intestine. The microorganisms are found in the deep layers of the mucosa as well as in ulcers. They have been isolated also from the regional lymph nodes. In contrast to the typhoid bacillus, *Shigellae* usually do not invade the blood stream and in the vast majority of cases of bacillary dysentery bacteremia neither precedes nor complicates the malady. Occasional cases of bacteremia caused by *Shigellae* (particularly *S. alkalescens*) have been encountered. The literature on this subject has been reviewed by Rothman (141), Haynes (85, 86), as well as Dodd and Swanson (34).

The question, then, arises: How do dysentery bacilli, localized in the intestinal tract and possibly in the regional lymph nodes, bring forth the characteristic lesions? No final answer can as yet be given to this problem. The intestinal lesion in bacillary dysentery, at least as far as advanced cases are concerned, is diphtheritic and ulcerative in nature. Undoubtedly, toxins or toxic products play an important role in the production of these lesions. As early as 1906, Flexner and Sweet (56) showed that injection of Shiga bacillus toxin into rabbits causes intestinal lesions. Interestingly enough, the toxin failed to do so when brought directly into the intestinal canal. These authors concluded from their experiments that the toxin is excreted in rabbits (and probably in man as well) by the intestine, while, being injured by the act of elimination, reacts by the development of inflammation. Fenner and Bernheim (133) recently advanced a new theory pertaining to the pathogenesis of the intestinal lesions in bacillary dysentery. On the basis of experimental observations they concluded that these lesions are similar to those produced by stimuli causing a shock-like state. Shiga toxin causes such a change, characterized by a rise of the hematocrit and specific gravity of the whole blood. As a result, there occurs a compensatory vasoconstriction in the duodenum of the dog and the cecum

of the rabbit. Whether the lesions in bacillary dysentery of man, too, are the end-result of a pronounced homeostatic vasoconstriction, remains to be determined.

THE CARRIER PROBLEM

The importance of carriers for the spread of infectious diseases in general hardly can be overrated. In Shigellosis, too, carriers play an important role in the dissemination of the causative agent. Two types of carriers may be distinguished; the healthy carrier, who, so far as it is possible to ascertain, did not previously suffer from Shigellosis and the convalescent carrier, who continues to excrete dysentery bacilli after having recovered from the disease. A critical investigation into the *Shigella* carrier problem was undertaken during World War I by Fletcher and MacKinnon (55). Of 935 persons, 2.78% excreted Shiga and Flexner dysentery bacilli for more than three months after the onset of the illness. More recently, Watt, Hardy, and De Capito (173) observed 80% convalescent carriers among 103 cases of Shigellosis. These individuals harbored dysentery bacilli up to one year after recovery. In another series of 163 persons, convalescent carriers were observed in 67% of the cases; Flexner, Sonne, and Newcastle bacilli were encountered.

It is particularly noteworthy that the carrier rate may be quite high among contacts with positive cases. Watt, Hardy, and De Capito, for example, found 28% carriers in such a group. In a military unit, where diarrheal disease was endemic, the carrier rate was 10% among men officially well. Persons harboring dysentery bacilli for more than one year were relatively infrequent.

It has been known for a long time that carriers of dysentery bacilli are particularly dangerous as inmates of institutions. Hardy and associates (77) and Watt and associates (174) examined 13,356 stool cultures obtained from inmates of institutions in New York, Vermont, Georgia, New Mexico, and Puerto Rico and isolated dysentery bacilli in 6.6% of the specimens. It is interesting to note in this connection that the carrier rate was found to be considerably higher than the rate of diarrheal disease.

With respect to healthy carriers, Watt, Hardy and De Capito (173) found among 6,324 individuals in New Mexico, Georgia, and Puerto Rico 3.8% carriers and among 1,659 persons examined in New York City only 0.1% carriers. Vaccaro, Meneghello, and Nino (169) reported from Chile an incidence of healthy *Shigella* carriers of 1.33%. In their experience carriers occurred only among children.

Attention should be called to the fact that persons may excrete dysentery bacilli at irregular intervals. Obviously, repeated stool examinations may be necessary to detect these cases.

PREVENTION OF AND IMMUNIZATION AGAINST BACILLARY DYSENTERY

Most important for the prevention of bacillary dys-

entery is a high standard of sanitary conditions in the community, state, and country. To prevent the dissemination of dysentery bacilli, the fecal excretions of patients suffering from bacillary dysentery should be properly disinfected. When indicated and feasible, these patients should be isolated. Therapy with sulfonamides may result in the eradication of dysentery bacilli from the intestinal tract. Carriers should be recognized and properly treated. It is of greatest importance that fecal contamination of water, milk, and other foods be prevented. Extermination of flies may aid in the control of this disease.

During the last few years, attempts were made to prevent dysentery in potentially exposed individuals by the prophylactic administration of sulfonamides. For example, Lucchesi and Gildersleeve (104) employed sulfaguanidine for this purpose. Among 45 intimately exposed patients in a hospital treated with the drug none developed dysentery, whereas of 48 less intimately exposed and untreated cases, four contracted the infection. Favorable results in the control of bacillary dysentery by means of sulfaguanidine have been reported by Hardy, Watt, Peterson, and Schlosser (82), as well as by Scott (153). Such procedures may be of greatest value in institutions.

Active immunization against Shigellosis was studied many years ago and has been reinvestigated during the past war. One of the main obstacles in active immunization has been the toxicity of the antigens used. Another complication arises from the fact that so many different types of dysentery bacilli are encountered in human infections. Finally, it is by no means easy to appraise accurately the efficacy of immunizing agents.

Claims made by investigators many years ago have not been generally substantiated. Shiga (156) stated that among 10,000 persons immunized with an antigen-antisera mixture the fatality rate was practically nil, whereas it amounted to 30% to 40% among the non-immunized individuals. This immunization, however, did not reduce the morbidity rate. A preparation containing toxin, antitoxin, as well as killed dysentery bacilli (*Dysbakta*) has been widely used in past years. Success as well as failure has been reported.

The problem of active immunization against Shigellosis has undergone a change in recent years. Shiga infections do not appear to be as serious as formerly and considerably more information is now available pertaining to the antigenic structure of the organism and the distribution of various species and types of dysentery bacilli.

With respect to active immunization against the exotoxin of the Shiga bacillus, formaldehyde-treated Shiga toxin (toxoid) has been employed as an immunizing agent. This material, which is less toxic than the original toxin, has been recommended for use by Dumas, Ramon, and Bilal (39). Olitzky and Bichowsky (127) prepared a Shiga toxoid from cultures of a Shiga bacillus on a semi-synthetic medium. Injection of small quantities of this toxoid absorbed on

alum engendered protective antibodies in rabbits. Olitzky and Koch (129) used a Shiga toxoid in 1,400 individuals and found that it did not produce any serious side-effects and, indeed, may have been of prophylactic value.

Various vaccines and antigens derived from dysentery bacilli have been studied during recent years. Attempts to decrease the toxicity of such preparations have also been made. Olitzky (125) reported that suspending the organisms in almond oil results in a lowering of toxicity. Attempts to increase the antigenicity of vaccines have also been undertaken. Halbert, Mudd, and Smolens (73) observed that the antibody response of mice and rabbits to a Flexner vaccine suspended in a saline-in-mineral-oil immersion may be considerably prolonged and often elevated compared to the vaccine suspended in saline solution.

Recently Cooper, Tepper, and Keller (32) prepared *Shigella* vaccines and immunized children. These authors found that their vaccines engendered protective antibodies and that a booster vaccination, administered one year later, caused a rapid increase in the titer of these antibodies. To what extent these vaccines may prevent natural Shigellosis, remains to be determined.

Shaughnessy, Olsson, Bass, Friewer, and Levinson (155) prepared an antigen consisting of different types of dysentery bacilli (Flexner, V, W, and Z, Boyd 88, *S. sonnei*, and *S. schmitzii*). The vaccine was exposed to ultraviolet rays and heated in a water bath at 62° C. for one hour. Dysentery vaccines, inactivated by exposing continuously flowing thin films of organisms to a powerful source of Schumann ultraviolet rays for a fraction of a second, did not cause severe reactions in man and evoked a significant degree of immunity in mice. However, human volunteers, who had been vaccinated with this antigen, failed to show immunity against experimental *Shigella* infection, in spite of the facts that the vaccine had elicited in them a definite increase in mouse-protective antibodies and that mice treated likewise showed a high degree of immunity. It is interesting to note in this connection that virulence of a particular strain to mice did not parallel a similar degree of virulence to man.

Goebel, Binkley, and Perlman (67) attempted to isolate from *S. paradyenteriae* antigenic components which play a significant role in the pathogenesis of the disease and may be used for active immunization. The toxic constituent of the antigenic complexes could not be inactivated without simultaneous destruction of its antigenic properties. The antigenic material consists of phospholipid-acetylated carbohydrate-protein complexes. It is interesting to note that following degradation the toxic constituent is found associated with the protein or the carbohydrate component. Human volunteers were inoculated with the specific somatic antigen of Type V Flexner dysentery bacillus. The antigen caused reactions which were no more severe

than those observed following injection with a typhoid-paratyphoid vaccine. The subjects developed a high titer of agglutinins and mouse-protective antibodies. It remains to be seen whether or not such an immunizing agent will induce active immunity in man. It also remains to be determined whether such an antigen will engender immunity against heterologous types of dysentery bacilli. Obviously, similar antigens could be prepared from other *Shigella* organisms and could be used according to the incidence of the various types of dysentery bacilli in a particular area. It is obvious, therefore, that the problem of active immunization against Shigellosis has not as yet been solved satisfactorily, although distinct advances have been made in this field during recent years.

CHEMOTHERAPY

It is generally agreed that the sulfonamides are the drugs of choice in the specific treatment of Shigellosis. *In vitro*, various sulfonamides exert bacteriostatic activity against dysentery bacilli. That strains of dysentery bacilli may become resistant to these drugs has been shown by Cooper and Keller (30, 31). The investigations by these investigators, furthermore, revealed a fact of possible clinical significance, namely, that a particular strain may be resistant to one, but not to another, sulfonamide compound. That these drugs are effective also in animals, experimentally infected with *Shigella* organisms, has been shown by several investigators. Dack and Hoskins (33) studied the effect of sulfaguanidine in experimental bacillary dysentery of *Macaca mulatta*. It is beyond the scope of this presentation to discuss the numerous reports on the efficacy of sulfonamides in the treatment of bacillary dysentery in man. Of the sulfonamides, the soluble compounds sulfathiazole, sulfadiazine, sulfamerazine, sulfapyrazine, sulfamethazine, and others, and the rather insoluble compounds sulfaguanidine, sulfasuccidine, sulfathaladine have been used.

Hardy and Watt (78) recommend for the treatment of Shigellosis sulfadiazine or sulfapyrazine, followed, if indicated, by sulfasuccidine. It may be pointed out that treatment with these drugs does not always result in clinical cure, nor does it always bring forth the elimination of dysentery bacilli.

As mentioned before, sulfonamides are also used successfully in the treatment of *Shigella* carriers (Hardy, Watt, Peterson, and Schlosser (82); Hoagland, Harris, and Raile (88), and others).

With respect to the presently used antibiotics, no evidence has become available to indicate that these drugs can be employed successfully in the treatment of Shigellosis. It is conceivable that streptomycin may be of value in certain selected cases, such as septicemia, and the possibility exists that antibiotics may be found in the future which are effective against *Shigellae* and which can be used in bacillary dysentery.

SERUM THERAPY

Since the advent of chemotherapy, treatment of bacillary dysentery with immune serum has lost con-

siderably in importance. Theoretically, the following antibodies are available: antitoxins, neutralizing the exotoxin of the Shiga bacillus and the endotoxins of the various dysentery bacilli, as well as antibodies against the dysentery bacilli themselves. Many years ago, Shiga studied the effects of Shiga antitoxin and claimed that it reduced the fatality rate by more than 50%. Subsequent investigations, however, have cast considerable doubt on the value of Shiga antitoxin. This serum is very rarely used at the present time in this country and a critical appraisal of its clinical value has to be deferred. Serum containing antibodies which neutralize endotoxins of Shiga and Flexner dysentery bacilli has been used, but the reports on its efficacy are contradictory. The use of serum from convalescents and immunized donors has been recommended by Felsen (48) and by Turell (168).

Serum as a therapeutic agent should not be entirely forgotten. Weil and McFarlane (181) have shown that prophylactic administration of type-specific antibodies to chick embryos, which have been infected experimentally with different types of *S. paradyenteriae*, was distinctly effective. The use of type-specific sera, therefore, remains a possibility in the treatment of human Shigellosis. Furthermore, attempts have been made recently by various investigators to determine the antigens and toxins of dysentery bacilli as a basis for the preparation of more potent antibacterial as well as antitoxic sera (Steabben and others 159-a).

BACTERIOPHAGE THERAPY

Bacteriophage, the lytic agent discovered by Twort and d'Herelle, has been used for the identification of dysentery bacilli (see below) and for the treatment of bacillary dysentery. The reports concerning its therapeutic efficacy, however, are conflicting. During the last few years, the action of *Shigella* bacteriophage *in vivo* has been re-investigated. Perez (134) as well as Morton and Perez-Otero (112) found that bacteriophage against *S. paradyenteriae* Flexner type X increases in experimentally infected mice. It is noteworthy that no such multiplication took place in mice injected with phage-insusceptible dysentery bacilli. Morton and Engley (110), in a parallel study, showed that phage which is effective *in vitro*, may protect mice against subsequent infection or even influence favorably an existing Shigellosis. Protection was achieved even against 10,000 minimum lethal doses. Treatment with bacteriophage proved to be effective provided that the administration of the therapeutic agent was delayed not more than three hours after the injection of the bacteria. In agreement with these findings are the observations of Dubos, Straus, and Pierce (38) to the effect that bacteriophage multiplies in the brain of mice injected intracerebrally with *S. dysenteriae* and that under suitable conditions, bacteriophage therapy may prevent a fatal outcome of the infection. Rakieten and Rakieten (136), too, observed the protective action of bacteriophage in chick embryos infected with *S. paradyenteriae*. In this

connection, it is worthy of note that bacteriophage either terminated or prevented Flexner dysentery in *Macacus rhesus* monkeys (Sandholzer 145). On the basis of these findings and of favorable clinical results (for example, Murray 113, Haler 74, Compton 28, and others) and in spite of disappointing results reported by others, type-specific or polyvalent *Shigella* bacteriophage should be re-investigated in human Shigellosis, in order to evaluate this agent under carefully controlled conditions. It may be mentioned in this connection that sulfanomides do not interfere with the lytic action of *Shigella* bacteriophage and may even suppress the development of phage-resistant organisms (Neter 116). According to the Russian investigator Yermoleva (195) the combined treatment of dysentery with sulfapyridine and bacteriophage yielded good results.

THE MICROBIOLOGICAL DIAGNOSIS OF SHIGELLOSIS AND DIAGNOSTIC PROCEDURES

The Bacteriological Diagnosis of Shigellosis. Collection of specimens: In the vast majority of cases, the bacteriological diagnosis of Shigellosis depends upon successful isolation of dysentery bacilli from the feces. Stool specimens, if feasible, should be obtained during the very first few days of the malady. In hospitals, a specimen should be sent to the laboratory without delay. Particles containing mucus or blood or both are used for examination. It has been shown that material obtained by means of swabs from the rectum are eminently useful for bacteriological study. Hardy and Watt (78) who have had very extensive experience with the rectal swab method, recommend the following procedure.

"A heavy fecal inoculum may and should be applied to highly selective media. It is unnecessary to use a bacteriologic loop for the streaking of *S. S.* agar plates; an ordinary cotton-tipped applicator is quite satisfactory. This makes it practicable to collect specimens by rectal swabs and to inoculate the plate immediately by "painting" the entire surface of the agar with the swab. In infants the applicator alone may be used and is satisfactory. For older children and adults the fecal inoculum may be obtained by the use of a short (4 1/2 inches) rubber tube of small diameter having within it the usual applicator with a compact cotton tip. The distal end of the tube is cut at a bevel and its external surface lubricated before use. For insertion the tip of the applicator is held just proximal to the opening of the tube. The tube and swab are readily inserted well beyond the sphincter and the swab is then exposed by withdrawing the tube slightly. The specimen is obtained by rotating the swab as it is moved to contact the mucosa at different points. Usually it becomes coated with feces or muco-purulent material."

Material obtained during proctoscopic or sigmoidoscopic examinations is also very useful for bacteriological examinations. In cases of extra-intestinal infection, urine, blood, pus, etc., has to be submitted for bacteriological study.

PRESERVATION OF STOOL SPECIMENS FOR BACTERIOLOGICAL EXAMINATION

If fecal specimens or rectal swabs can not be examined immediately after they have been procured, it

is advisable to add the material to a preserving or enriching fluid. Otherwise, it may be very difficult or even impossible to recover the pathogen. Such a preserving fluid has been described by Bangxang and Eliot (9). It consists of buffered saline solution (pH 8.5) containing 1% sodium citrate and 0.5% sodium desoxycholate. This fluid has been used successfully by the author. Selenite-F broth (see below) is also valuable. The preserving fluid of Sachs may be used. It consists of 30% glycerine in physiological saline solution, adjusted with sodium phosphate to a reaction of pH 8; it is tinted with phenol red indicator. This mixture is put up in 10 cc. quantities in small screw-capped bottles and it should be used only if of pink color. Sachs (143) has shown that a buffered glycerine saline solution is distinctly superior to a neutral glycerine saline solution. The solution is prepared as follows:

1. To 1,000 cc. glycerine add 2,000 cc. saline solution.
2. To this mixture add sufficient phenol red solution to match the standard indicator (phenol red) tubes in the pH set.
3. Add sufficient Na_2HPO_4 to adjust reaction to pH 8.0.
4. Tube off in 10 cc. bulks in one ounce screw-capped bottles.
5. Sterilize either fractionally or for ten minutes in the autoclave at ten pounds pressure.

The pH after sterilization will be approximately 7.4. The New York State Department of Health recommends a 30% glycerol in 0.6% salt solution buffered with phosphate. Theoretically, 3.1 grams of dipotassium phosphate, anhydrous, and 1 gram of monopotassium phosphate, anhydrous, are required per liter. If necessary, adjust the pH with normal HCL or Na-O. H.

Kligler, Oleinik, and Czazkes (94) suggest adding formaldehyde (1:10,000, 1:7,500) to fecal specimens, in order to inactivate any *Shigella* bacteriophage, if present, and, thus, increase the percentage of positive isolations. Felsenfeld (51) recommends the addition of 5 mg. of p-aminobenzoic acid to 100 cc. of enriching fluid, in order to counteract any sulfonamide present in the specimen.

INOCULATION OF CULTURE MEDIA

Suitable culture media are seeded with the specimen. Boyd (19) recommends to wash the mucus in sterile physiological saline solution. This procedure may not be necessary if selective culture media are employed. Since frequently it is not known beforehand how many microorganisms are present in a specimen, it is advisable to inoculate the differential culture media in the following fashion: approximately one-third of each agar plate is seeded directly with the specimen; then, the bacteriological loop is sterilized and cooled and material from the inoculated area is taken up and seeded on the second third of the media; this material from the second inoculation is then taken up for seeding of the remaining part of the plate. Thus, in the majority of cases it is possible to produce isolated colonies. The selective culture media are heavily seeded; the entire surface of the agar is "painted" with the rectal swab.

SELECTION OF CULTURE MEDIA

During the last few years, remarkable advances have been made in the perfection of culture media suitable for the isolation of enteric pathogens. As a result, selective-differential culture media, which are inhibitory to the saprophytic flora and yet support the growth of pathogens, are now available. The most important selective culture media suitable for the isolation of *Shigellae* are S. S. agar (Difco), desoxycholate citrate agar, and desoxycholate agar (Baltimore Biological Laboratory). The older differential culture media such as Endo agar, MacConkey agar, eosin-methylene blue agar, lithium chloride Endo agar and others support the growth of both saprophytes and pathogens. Regarding the various culture media and their preparation, the reader is referred to "Diagnostic Procedures and Reagents" published by the American Public Health Association (1).

In order to obtain the best possible results, it is recommended that both selective and differential culture media be used. One of several reasons why one of the older non-selective culture media should also be used is the fact that *S. sonnei* in phase II may be inhibited on the selective media, but grows on Endo or MacConkey agar. The value of culture media containing sodium desoxycholate has been shown first by Lefson (101) and has been confirmed by numerous investigators, including Paulson (132); Rose, and Kolodny (140); Irons, Bohls, De Shazo and Hewlett (90); Felsenfeld and Young (52); Hardy, Watt, De Capito, and Kolodny (81); Coleman (27); Mollov, Winter, and Steinberg (107); Neter and Clark (121), and others. The *Shigella*-*Salmonella* agar has been used extensively both in the United States and abroad. Its efficacy has been attested by Pott (135); Mayfield and Gohar (106); Mollov, Winter, and Steinberg (107); Felsenfeld and Young (52); Rose and Kolodny (140); Hardy, Watt, and De Capito (80); Neter and Clark (121); and others. Wilson and Blair (191) described a tellurite-iron-sulfuric acid medium for the isolation of *S. dysenteriae*, which was found very satisfactory by Thomas and Hulme (164). According to Felsenfeld (51) and others, this medium offers no advantage over S. S. and desoxycholate citrate agar.

In addition to the culture media just mentioned, certain enriching fluids have been used with success, particularly selenite-F broth. Tetrathionate broth seems to be somewhat less efficacious in the isolation of *Shigellae*. The enriching fluid is incubated for 18 to 24 hours at 37° C. and sub-cultures are made on S. S., desoxycholate citrate, and MacConkey agar.

In summary, then, the following facts may be re-emphasized.

1. No one single culture medium has yet been devised which yields 100% isolations of pathogens.
2. The highest percentage of successful isolations is achieved by the simultaneous use of selective culture media, differential culture media and enriching fluids.

For the isolation of *Shigellae*, the author recommends the use of S. S. agar, desoxycholate citrate agar, MacConkey agar, selenite-F broth and the enriching fluid of Bangxang and Eliot.

In passing, it should be mentioned that other culture media must be added for the isolation of other enteric pathogens. For example, bismuth sulfite agar should be used in the examination of specimens for the presence of typhoid and paratyphoid bacilli. Certain strains of *Shigellae* may grow on this medium, according to Galton and Collins (62).

FISHING OF SUSPICIOUS COLONIES

After incubation of the culture media at 37° C. non-lactose fermenting colonies are fished for the purpose of

Identification. It should be stressed that more satisfactory results are obtained if several suspicious colonies are examined. In this laboratory, suspicious colonies are fished from every culture medium and in addition, several colonies on a single agar plate may be examined. Furthermore, it is advisable to reincubate the agar plates for an additional 24 and 48 hours. As pointed out by Mayfield and Goerber (106), pathogens may be isolated after prolonged incubation from agar plates which did not yield suspicious colonies after 24 hours.

IDENTIFICATION OF SHIGELLAE

Non-lactose-fermenting colonies are fished for further study with regard to the cultural, biochemical, and antigenic characteristics of the microorganisms. A few comments may be made concerning some of the methods used and the interpretation of the results obtained. Then, a summary will be given of the recommended steps to be taken to accomplish identification of the organisms.

A. MOTILITY

In order to determine whether or not the organism is motile, the culture should be grown in a suitable medium. Some bacteriologists recommend the use of infusion broth, others prefer a semisolid culture medium. Edwards and Brunner (40) have described an excellent motility medium. It should be emphasized that some strains may be motile when grown at room temperature and that motility can not be recognized in a culture grown at 37° C. Furthermore, it should be mentioned that in a particular culture, numerous bacilli may be non-motile and only occasional bacterial cells may show motility. Care must be taken not to mistake molecular movement for motility. That this examination sometimes presents difficulty can be seen from the fact that Shiga himself described his bacillus as motile. Ordinarily, *Shigellae*, with the exception of the Newcastle bacillus, lack flagella and, therefore, are not motile. However, certain strains may acquire the ability to become motile following serial transfers in semisolid agar.

B. BIOCHEMICAL ACTIVITIES

Of distinct aid in the identification of unknown strains is the determination of the growth requirements and biochemical activities of unknown strains. The action upon urea, glucose, lactose, sucrose, maltose, mannitol, salicin, rhamnose, xylose, dulcitol, adonitol, arabinose, and sorbitol should be determined. Furthermore, tests should be carried out to ascertain whether or not the strain produces indole, forms H_2S , and grows in Koser's citrate medium. In contrast to hitherto expressed statements, certain strains of *S. paradyenteriae* and *S. alkalescens* may form H_2S . Gelatin liquefaction, too, which is always negative with *Shigellae*, may be determined.

Aside from their action upon certain test substances, the members of the genus *Shigella* may be conveniently, though roughly, divided into large groups according to the Eijkman and Wood reactions. The culture medium used for the determination of trimethylamine oxide reduction (Wood test) can be procured from Lederle Laboratories. This test, originally described by Wood, has been shown to be quite useful and gives positive results with the majority of strains of *S. sonnei*, *S. dispar*, and *S. alkalescens*, whereas negative results are obtained with *S. dysenteriae* (Shiga), *S. schmitzi*, and *S. paradyenteriae*. (Wood, Baird, Keeping (193); Wood and Baird (192); Wood and Keeping (194); Well and Black (197)).

The Eijkman test is based upon growth or absence of growth at 45.5° C. and acid formation in the Eijkman medium containing glucose. The culture medium may be procured from Difco Laboratories. According to Stuart and Rustigian (161), negative Eijkman reactions (no growth, no acid formation at 45.5° C.) are not obtained with *S. dysenteriae* (Shiga), *S. schmitzi*, *S. sp.* (Newcastle type), and *S. paradyenteriae*. *S. alkalescens*, *S. sonnei*, and *S. dispar* give positive reactions.

To hasten the identification of unknown strains, it is advisable to transfer suspicious colonies from the original agar to triple sugar iron agar. This culture medium may be procured from Baltimore Biological Laboratories and Difco Laboratories. It contains glucose, lactose, as well as sucrose and yields information regarding H_2S formation. *Shigellae* cause acid formation in the butt, but not on the slant, and most strains fail to form H_2S . Thus, this single culture medium makes it possible to select cultures for further study and to exclude others as not belonging to the genus *Shigella*.

Suspicious colonies may then be seeded from the triple sugar iron agar medium into a suitable urease test medium, which can be procured from Baltimore Biological and Difco Laboratories. *Shigellae* do not ferment urea.

Strains which, according to the tests performed up to that point of investigation, are suspicious of being *Shigellae* are then inoculated into the complete "biochemical set;" material from the triple sugar iron agar may also be used, as will be shown presently, for antigenic analysis.

The action of the strains upon test substances such as glucose, lactose, mannitol, salicin, etc., should be observed for three weeks. In this laboratory, inverted fermentation tubes are used with glucose and mannitol, in order to ascertain any gas formation; since some of the test substances may be broken down by autoclaving, broths containing lactose, maltose, sucrose, rhamnose, and xylose are sterilized by filtration. Phenol red is an entirely satisfactory indicator. A summary of the biochemical reactions of *Shigellae* as a key to classification of unknown strains is presented in tables I, II, IV.

Observation of the biochemical activities of unknown strains is of practical importance, but should not be used as the sole criterion for identification. It is imperative to determine also the antigenic structure of suspicious strains.

TABLE IV

SUMMARY OF

BIOCHEMICAL CHARACTERISTICS OF SHIGELLAE

- A. Mannitol-negative, lactose-negative group
 - I. Glucose: acid
 - 1. Indole-negative
 - a. Arabinose-negative: *S. dysenteriae* (Shiga)
 - b. Arabinose-positive: Sachs types Q771, Q454, and Q1030 (see table I)
 - II. Glucose: acid and gas:
- B. Mannitol-positive, lactose-negative group
 - Flexner-Boyd-*S. alkalescens* group
- C. Mannitol-positive, lactose-positive group
 - I. Indole-negative: *S. sonnei*
 - II. Indole-positive: *S. dispar*

C. ANTIGENIC STRUCTURE

Although *Shigellae* have been identified serologically by means of precipitation and complement fixation reactions, the agglutination test has been shown to be the most practical method.

In diagnostic laboratories, it is often imperative to give a preliminary diagnosis as soon as possible. To this end, a suspension may be made from the slant of the triple sugar iron agar (or even from the original agar) for agglutination tests with polyvalent *Shigella* serum. Quite often, then, it is possible to notify the clinician of a positive finding one to three days after the specimen was submitted.

The distribution of diagnostic polyvalent *Shigella* sera should be promoted, particularly by Health Departments.

The New York State Health Department, for example, supplies such a serum. A very reliable serum may be procured also from Lederle Laboratories. Obviously, it should be kept in mind that such a polyvalent serum may not agglutinate some of the rarer types of the genus. Consequently, a negative test does not necessarily indicate that the strain under consideration is not a dysentery bacillus. The specificity of these sera must be clearly established, if reliable results are to be obtained.

The slide agglutination tests as recommended by Well and others (179), proves to be accurate and time-saving. It should be noted that certain strains are agglutinated only if the suspension was previously heated at 100° C. for half an hour.

If agglutination has been obtained with a polyvalent *Shigella* serum, type- or species-determination can be accomplished by the use of type- or species-specific antisera. Although such diagnostic sera are commercially available from several manufacturers, the most complete set of sera is supplied by Lederle Laboratories. Type- and species-determinations should be done on a much larger scale than heretofore, and it is to be expected that such determinations may yield important information on the distribution of *Shigellae* and the epidemiology of Shigellosis.

For the correct interpretation of these agglutination tests, it is important to keep in mind that antisera against rarer types may not be available and that cross-reactions occur between *Shigellae* and other types or species or the family Enterobacteriaceae. To mention only a few examples of these cross-reactions: *S. paradysenteriae* V shares an antigenic component with certain *Salmonella* strains, particularly with *Salmonella onderstepoort*. Boyd's type P143 shares an antigen with certain paracolon strains (Ferguson and Wheeler, 53); as a matter of fact, if biochemical tests had been omitted, these paracolon strains would have been identified erroneously as *S. paradysenteriae*. Other cross-reactions have been encountered by Bornstein, Saphra, and Daniels (17); Saphra and Silberherg (146); Wheeler (183); Edwards, Cherry, and Bruner (41); as well as Stuart, Rustigian, Zimmerman, and Corrigan (162). Wheeler (184) described in detail the serological identification of dysentery bacilli, making use of a slide agglutination test. Formalized antigens and titrated and absorbed typing fluids were employed. The method proved satisfactory in the examination of more than 1,000 strains.

Gonzalez and Otero (68) described a method for the identification of *S. paradysenteriae* by means of a precipitation test. It appears that this method, although accurate, is more time-consuming than the slide agglutination test.

D. SUSCEPTIBILITY TO SPECIFIC BACTERIOPHAGES

Thomen and Frobisher (166) have shown recently that the majority of species and types of the genus *Shigella* can be identified by the use of species- and type-specific bacteriophages. It seems possible that this method may be used to advantage as a supplement to other serological tests. Sehade and Caroline (148) reported a method for the preparation of *Shigella* bacteriophage in a dry and stable form. It remains to be seen whether such a preparation may be used successfully for diagnostic and therapeutic purposes.

THE SEROLOGICAL DIAGNOSIS OF SHIGELLOSIS

Far less satisfactory and far more difficult than the bacteriological diagnosis of Shigellosis is the serological diagnosis (Widal test). The Widal test does not allow an early diagnosis, because agglutinins may not be formed by the patient before the sixth to twelfth day after the onset of the disease. In some cases, the

infection may not even engender any antibodies. Furthermore, human serum may contain physiological agglutinins sometimes even in high titer, a fact, which renders the interpretation of this test extraordinarily difficult. Erroneous conclusions have been drawn on the basis of incorrect interpretation of the results. It is essential in carrying out the Widal test to (a) use standardized suspensions of known agglutinability; (b) employ a standardized procedure (temperature, time of incubation, etc.); (c) know the titer of normal agglutinins for the respective suspensions; and (d) use proper positive and negative controls. Obviously, a fairly large number of different species and types of *Shigellae* should be employed.

Reportedly, the Widal test in cases of Shiga bacillus infections may be positive in titers of 1:100 to 1:500. Normal sera, on the other hand, supposedly do not agglutinate this organism in titers above 1:50. A rise of the agglutinin titer during the illness, followed later by a decline, is considered as suggestive of a previous Shiga bacillus infection. It should be noted, however, that Thomas and Levine (165) found a relatively high titer of Shiga bacillus agglutinins in the serum of prenatal cases.

With respect to the antibody response of patients infected with the Schmitz bacillus, it should be noted that patients may develop agglutinins in high titer (up to 1:3,000); Schleifstein and Coleman (150) reported failure of antibody response in only 15 out of 200 cases.

Sachs (144) has demonstrated that patients suffering from Shigellosis due to the Sachs types may develop agglutinins in significant titer. It is interesting to note that 200 random serum specimens failed to agglutinate these organisms.

According to Clayton and Warren (25, 26), patients suffering from Shigellosis due to the Newcastle bacillus may produce agglutinins against this particular organism in titers from 1:50 to 1:500. In their experience, normal sera failed to agglutinate this organism.

In Sonne bacillus infections, too, antibodies may be engendered in significant titers. The agglutinin titer is rarely higher than 1:50 in sera from normal individuals. Fyfe (61) reported antibody formation in the majority of his cases; the antibodies appeared between the sixth and twenty-seventh day of the illness and the titers ranged from 1:25 to 1:6,000.

With respect to the antibody response of persons suffering from infection due to Flexner-Boyd types of organisms, attention should be called to the fact that type-specific antibodies may appear in the serum in certain cases and that individuals without history or evidence of Shigellosis may have in their blood fairly high titer of agglutinins. Schwabacher, Ross, and Carruthers (152) determined the titers of *Shigella* agglutinins in normal sera and found titers of 1:160 and above against certain Flexner types. It remains to be determined whether or not primary antigens

TABLE V

SUMMARY

ISOLATION AND IDENTIFICATION OF SHIGELLAE

0 hour	a) Procure suitable specimen. b) Seed	S. S., D. C. agar and differential agar, e. g. MacConkey agar.	Selenite-F broth.
		↓	↓
18-24 hours	c) Fish negative colonies to triple sugar iron agar.	Continue incubation.	Subculture on S. S., D. C. and MacConkey agar.
	↓	↓	↓
48 hours	d) Seed biochemical set with suspicious cultures. Use material from slant also for slide or tube agglutination test with polyvalent <i>Shigella</i> serum; if positive, use monovalent sera. Give preliminary diagnosis.	Fish negative colonies to triple sugar iron agar.	Continue as (c), if indicated.
	↓	↓	↓
72 hours to 3 weeks	e) Continue observations and give final diagnosis (d) on identified strains. Send unidentified, but suspicious cultures, to a special laboratory.	Continue, if indicated, as (c).	Continue as (c), if indicated.

may be used as antigens instead of bacterial suspensions for diagnostic precipitation tests.

THE DIAGNOSTIC SIGNIFICANCE OF THE PRESENCE OF SHIGELLA BACTERIOPHAGE IN PATIENTS SUFFERING FROM SHIGELLOSIS

Failure to isolate dysentery bacillus from feces of the patient may be due to the presence of specific bacteriophage. It is for this reason that inactivation of the lytic agent in such specimens has been advocated as a means of increasing the percentage of positive isolations (Kligler, Oleinik, and Czazkes 94). On the other hand, the presence of *Shigella* bacteriophage has been interpreted as indicative of past or present Shigellosis (Feenister 46, Wheeler and Burgdorf 186, Felsen 47 and others). However, it must be emphasized that the demonstration of a phage does not give adequate evidence of a specific infection. Attention may be called to the observation of Rhodes and Ludlam (139), who found bacteriophage active against dysentery bacilli in municipal water supplies in Scotland, a bacteriophage, which could be propagated even in the presence of *B. coli*.

THE DIAGNOSTIC SIGNIFICANCE OF ALLERGIC REACTIONS

Several years ago, Silverman and Efrom (157) re-

ported that certain patients suffering from Shigellosis gave allergic reactions to *Shigella* vaccines. Until more extensive studies have been carried out with respect to the specificity and sensitivity of such tests, allergic reaction to *Shigellae* as a diagnostic test should be interpreted with great reservations.

SUMMARY AND OUTLOOK

Impressive strides forward have been made in the last few years in our knowledge of the genus *Shigella*. As outlined here, the methods used in the isolation and identification of dysentery bacilli have been considerably improved and can now be considered as satisfactory. Lagging behind these scientific advances is the application in many parts of the world of our knowledge of the diagnosis of bacillary dysentery. The problem of active immunization has not been solved, but advances have been made recently in this field. Chemoprophylaxis and chemotherapy yield satisfactory results. Thus, it may be concluded that the present scientific knowledge permits of rather effective control of Shigellosis, one of the important scourges of mankind.

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Statistical Analysis of Deaths from Diabetes in the District of Columbia for a Period of 42 Years --- 1903-1944 Inclusive

Preliminary Report and Analysis: A Comparison of Two 5-Year Periods --- 1903-1907 and 1940-1944

By

JOHN A. REED, A.B., M.D., F.A.C.P.*

WASHINGTON, D. C.

SCOPE OF ENTIRE STUDY

THE FULL STUDY, to be published at a later date, of all persons where diabetes was mentioned on the death certificate, will cover a period of 42 years from 1903-1944. The material for this study is taken from the death certificates as filed with the Division of Vital Statistics of the Health Department of the District of Columbia and signed by the attending physician at the time of death.

The survey of these deaths is divided into two general groups: first, those in which diabetes or a direct complication thereof is given as the immediate or primary cause of death; the second, those in which diseases other than diabetes are given as immediate or primary cause of death while diabetes is given as a secondary or contributory factor in the case.

All data which could be secured from a death certificate were considered and studied. The data recorded included: the total number of deaths for each year; the total number considered as deaths from diabetes or its complications; the total number considered as deaths from causes other than diabetes but having diabetes mentioned on the death certificates; sex studies; race studies; occurrence of gangrene, acidosis and/or coma, pneumonia, general infection, exhaustion, in the diabetic deaths; the occurrence of gangrene, tuberculosis and acidosis and/or coma in the group where death was from causes other than diabetes; age studies; division of home and hospital care; and finally an analysis of the causes of deaths in the group where diabetes was considered a secondary or contributory cause.

To complete this study, it would be ideal to have been able to have questionnaires distributed to the various attending physicians as to symptoms, duration of disease, and character of treatment. This was impractical.

SCOPE OF PRELIMINARY REPORT

The same data are considered in this preliminary report as in the entire report and a comparison made of these data for the two five year periods studied

* From the Department of Medicine. The George Washington University School of Medicine.

* Associate Clinical Professor, Department of Medicine. The George Washington University School of Medicine.

and reported. The first period 1903-1907 being roughly a period twenty years before the general use of insulin and the second period 1940-1944 being roughly a period twenty years after the release of insulin for general use. The year considered as the year of general release of insulin is 1923.

PRELIMINARY REPORT AND ANALYSIS

GENERAL STUDY OF TOTALS

The total number of deaths in the five year period 1903-1907 in which diabetes is cited is 187. The total number for the five year period 1940-1944 in which diabetes is mentioned is 1119, which is approximately five times greater than those recorded in the five year period 1903-1907.

The average population for the District of Columbia for the period 1903-1907 was 304,893 while the average population was 815,000 for the period 1940-1944, approximately $2\frac{2}{3}$ times as many people in the second five year period as in the first five year period. This then definitely suggests that the increase of population alone does not account for the increase in diabetes as recorded on death certificates. Furthermore, one must remember that there was an unusual war mushroom increase in population in the District of Columbia since in 1940 the population was 677,000 and in 1944, 900,000. It is to be noted that in 1940, 219 death certificates mentioned diabetes while in 1944, 227 death certificates mentioned diabetes, an increase of only eight cases.

Some attribute this apparent increase in diabetes to an actual increase in the disease. Others surmise more accurate diagnoses, more persons routinely examined, more extensive education of population, more "diabetic conscious" physicians, as some of the probable causes of the increase of recorded cases.

GENERAL DIVISION OF STUDIES

As mentioned, all cases in the two five year periods are divided into those whose death was recorded as primarily due to *diabetes or its complications* and those whose death was recorded as due primarily to *disease other than diabetes*, and diabetes only a secondary or contributory cause of death.

It is noted that 145 or 77.5% (see Table No. I) of the 187 cases in the first period 1903-1907 died pri-

marily of diabetes or its complications while 42 or 22.5% died of causes other than diabetes.

TABLE I
SUMMARY OF TOTALS FOR THE TWO FIVE YEAR
PERIODS 1903-1907 and 1940-1944

Year	Total Number	Deaths Primarily Due to Diabetes or its Complications	Deaths Due Primarily To Diseases Other Than Diabetes	Population of District of Columbia
1903	26	25	1	294,424
1904	35	30	5	299,659
1905	46	31	14	304,894
1906	26	23	5	310,129
1907	53	36	17	315,364
Grand Total	187	145	42	Average 304,893
		77.5% of the total	22.4% of the total	
1940	219	91	128	677,000
1941	179	51	128	750,000
1942	253	46	207	848,000
1943	241	64	177	900,000
1944	227	56	171	900,000
Grand Total	1119	308	811	Average 815,000
		27.5% (plus) of the total	72.4% (plus) of the total	

Compare these figures with the second five year period 1940-1944. In this period 308 or 27.5 plus % died of diabetes or its complications while 811 or 72.4 plus % died of causes other than diabetes.

The significance of these figures seems obvious to some authors. The better management of diabetes from a dietary standpoint as well as the use of insulin con-

trols the diabetic condition as indicated by blood sugar levels and urinary sugar excretions even in the presence of other fatal diseases and hence is considered a secondary rather than an immediate cause of death. Because of the improved dietetic and insulin therapy, the diabetic lives into older groups where other diseases appear and cause death. In our report under "Age Studies" such a conclusion is not substantiated.

SEX STUDIES (see Table No. II.)

In the first five year period 1903-1907 it is to be noted that 100 or 53.4% of the total 187 deaths were males while 87 or 46.5% of the 187 deaths were females.

TABLE II
SEX STUDIES

Year	All Cases		Primary Cause Diabetes		Causes Other Than Diabetes	
	M	F	M	F	M	F
1903	13	13	13	12	0	1
1904	17	18	13	17	4	1
1905	25	20	16	15	9	5
1906	14	14	14	12	11	2
1907	31	22	23	13	8	9
Totals	100	87	77	68	23	19
	53.4%	46.5%	53.1%	46.9%	54.7%	45.2%
1940	83	136	29	62	54	74
1941	64	115	16	36	49	79
1942	92	161	13	33	79	128
1943	96	145	29	35	67	110
1944	80	147	16	41	65	106
Totals	415	704	101	207	314	497
	37%	62.9%	32.7%	67.2%	38.71%	61.28%

In the second five year period 1940-1944 it is to be noted that 415 or 37% of the total 1119 deaths were males while 704 or 62.9% of the total 1119 deaths were females.

The same percentage is approximately obtained in

TABLE III
RACE STUDIES

Year	Primary Cause Diabetes				Causes Other Than Diabetes			
	MW	MC	FW	FC	MW	MC	FW	FC
1903	13	0	10	2	0	0	1	0
1904	11	2	14	3	4	0	1	0
1905	13	3	13	2	9	0	5	0
1906	12	0	11	0	1	1	2	1
1907	22	1	13	0	8	0	9	0
Totals	71	6	61	7	22	1	18	1
	48.8%	4.1%	42%	4.8%	52%	2.3%	42.5%	2.3%
1940	17	12	34	28	44	10	65	9
1941	10	5	19	17	38	11	62	17
1942	4	9	15	18	69	10	52	36
1943	20	9	18	17	18	8	75	31
1944	9	6	17	24	55	10	77	29
Totals	60	41	103	104	263	49	371	126
	19.45%	13.31%	33.44%	33.76%	52.67%	6.04%	45.74%	15.53%

a breakdown into the two divisions: namely, for the years 1903-1907, those who died of diabetes or its complications 53.1% males and 46.9% females; and those who died of causes other than diabetes 54.7% males and 45.2% females (see Table No. II); and for the years 1940-1944, those who died of diabetes or its complications 32.7% males and 67.2% females and those who died of other causes, 38.71% males and 61.28% females.

No reason is known from these studies for the change in the two five year periods.

RACE STUDIES (see Table No. III).

Of the total one hundred and eighty-seven cases recorded on death certificates as having diabetes in the years 1903-1907, 172 or 91.97% were white and 15 or 8.02% were colored. Broken down further, 49.73% were male white; 42.24% were female white; 3.74% were male colored; and 4.27% were female colored.

Of the total one thousand one hundred and nineteen cases recorded on death certificates as having diabetes in the years 1940-1944, 799 or 71.40% were white and 320 or 28.29% were colored. Broken down further 29.04% were male white; 42.35% were female white; 8.04% were male colored; and 20.55% were female colored.

In Table III these figures are broken down further. In 1903-1907, 48.8% of the total number of cases whose primary cause of death was diabetes were male white; 4.1% were male colored; 42% were female white; and 4.8% were female colored. While in the same period 52.3% of the total number of cases whose death was given as a cause other than diabetes but diabetes mentioned as a secondary or contributing cause were male white; 2.3% were male colored; 42.8% were female white; and 2.3% were female colored.

In 1940-1944, 19.48% of the total number of cases whose primary cause of death was diabetes were male white; 13.31% were male colored; 33.44% were female white; and 33.76% were female colored. While in the same period 32.67% of the total number of cases whose death was given as another primary cause but diabetes mentioned as a secondary or contributing cause, 32.67% were male white; 6.04% were male colored; 45.74% were female white; and 15.53% were female colored.

It is to be noted while 91.97% of the total diabetic deaths in 1903-1907 were white, the percentage of white population in the District of Columbia in the same period was only 70.13%; 8.02% deaths were colored while percentage of colored to total population was 29.86%.

In the period 1940-1944, 71.40% of the total diabetic deaths were white while the average percentage white to total population in the District of Columbia for the same period was 71.5%; 28.59% of the total diabetic deaths for the same period were colored and 28.5% of the total average population was colored for this five year period.

OCCURRENCE OF COMA, GANGRENE, ETC. IN THOSE WHERE DIABETES IS GIVEN AS A PRIMARY CAUSE OF DEATH

With the institution of insulin and probably a better dietetic management of the diabetic in 1922, improvement in the care of the diabetic was supposedly advanced. Have we prevented the occurrence of some of the severe complications of the diabetic by this improved management? Figures from this study seemingly do not bear out that the occurrence of coma and gangrene in the diabetic dying of this disease has diminished. In the five year period 1903-1907 of those dying of diabetes as a primary cause of death, 8.2% had gangrene recorded on the death certificate

TABLE IV
Study of Complications

Year	All Cases					Diabetes Considered as Primary Cause of Death				
	Gangrene	Tbc	Acidosis and/or Coma	Cancer		Gangrene	Pneumonia	General Infections	Acidosis and/or Coma	No Specific Cause Given
1903	1	0	11	0		1	0	1	11	3
1904	5	0	15	0		5	0	2	15	2
1905	5	1	20	0		1	0	0	20	5
1906	3	0	12	0		3	1	1	10	4
1907	3	0	17	0		2	0	2	15	6
Totals	17	1	75	0		12	1	6	71	20
	9%	0.5%	40.1%			8.2%	0.6%	4.1%	48.9%	13.7%
1940	26	4	42	1		23	5	11	38	14
1941	19	0	34	0		9	1	3	32	8
1942	23	6	30	7		9	1	1	27	7
1943	28	0	38	0		12	0	11	35	6
1944	14	2	43	1		6	1	2	37	10
Totals	110	12	187	9		59	8	28	169	45
	9.8%	1.07%	16.7%	.8%		19.1%	2.6%	9.09%	54.8%	14.6%

while in the period 1940-1944, 19.1% had gangrene recorded on the death certificate. In the five year period 1903-1907, coma and/or acidosis occurred in 48.9% of the cases (see Table No. IV) while in the period 1940-1944, coma and/or acidosis occurred in 54.8% of the cases. Surely in those who died of diabetes as the primary cause there does not seem to be any diminution of the two outstanding complications of diabetes, namely gangrene and coma and/or acidosis. Of course it is recognized that many living diabetics today never have these complications but those who died of diabetes as a primary cause seem to have had an increase in these two complications.

It is however to be noted that of all cases recorded as having died in the five year period 1903-1907 where diabetes was either recorded as the primary cause of death or contributory cause, 40.1% had coma and/or acidosis; while in the five year period 1940-1944 in all such cases recorded only 16.7% had coma and/or acidosis. This suggests that among those who die of primary diabetes, acidosis and/or coma is still a prominent complication, but in all cases having diabetes, this complication has been lessened.

Other complications recorded in the primary diabetic deaths for the first five year period 1903-1907 are as follows: 0.6% had pneumonia; 4.1% a general infection; and in 21.3% the term "exhaustion" was given as a contributory cause.

In the second five year period 1940-1944, 2.6% had pneumonia and 9.09% had a generalized infection. The term "exhaustion" has disappeared from the death certificate as a contributory cause in this five year period.

AGE STUDIES (see Table No. V)

The average age at death for all cases in the first five year period 1903-1907 is 59.7 years while the average age at death for all cases in the second five year period 1940-1944 is 59.6, seemingly the same for the two periods.

The average age at death of cases where diabetes is considered the primary cause of death in the first five year period 1903-1907 is 50 and the average age for the same group in the second five year period 1940-1947 is 54.6.

The average age at death of cases where primary cause is other than diabetes for the first five year period 1903-1907 is 69.4 and the average age for the same group in the second period 1940-1944 is 64.6.

Of these two groups it seems that longevity is increased in those cases where the death is primarily due to diabetes and decreased in those cases where death is due to causes other than diabetes. Explanation of this decrease may be made by subsequent study of the various causes of death other than diabetes.

Further age studies were made of the deaths due primarily to diabetes where coma, gangrene, and infections other than pneumonia were complications. In

TABLE V
AGE STUDIES

Further Age Studies in deaths due primarily to Diabetes and its complications.					
Year	Average Age of cases where Diabetes is considered primary cause of death.	Average Age of cases where primary cause of death is other than Diabetes.	Coma	Gangrene	Infections — excluding pneumonia
1903	55.0	81.0	48.2	75.0	50.0
1904	49.5	65.6	43.2	61.0	24.0
1905	46.8	69.6	42.4	66.0	48.0
1906	49.5	64.5	47.4	65.3	52.0
1907	49.5	66.5	46.4	56.5	60.0
Average Age	50.0	69.4	45.5	64.7	49.2
1940	55.5	65.5	49.0	66.4	50.6
1941	56.5	65.0	53.7	67.0	35.6
1942	55.9	63.9	54.9	59.2	51.8
1943	54.5	64.9	50.8	62.2	46.7
1944	50.9	64.0	48.4	63.4	53.3
Average Age	54.6	64.6	51.3	63.6	47.6

the first five year period 1903-1907 those who died primarily of diabetes and were complicated by coma, the average age was 45.5; complicated by gangrene the average age was 64.7; and complicated by infection other than pneumonia the average age was 49.2.

Similar age studies were made for the second five year period 1940-1944; complicated by coma in this period the average age was 51.3; complicated by gangrene the average age was 63.6; and complicated by infection other than pneumonia the average age was 47.6.

TABLE VI
Home and Hospital Care

Death Primarily Due to Diabetes		Death Due to Other Causes	
Year	Home Hospital	Home Hospital	
1903	21 4	1 0	
1904	24 6	3 2	
1905	28 3	10 4	
1906	18 5	5 0	
1907	26 10	16 2	
Totals	117 28	34 8	
	62.4 14.9%	18.1% 4.2%	
1940	24 67	61 67	
1941	14 37	55 73	
1942	9 37	89 114	
1943	10 54	70 107	
1944	14 42	66 105	
Totals	71 237	341 470	
	6.3% 21%	20.4% 42%	

TABLE VII

Studies of Primary Causes of Death in Individuals who
Had Diabetes Recorded as a Contributory or Secondary
Cause of Death

Primary Cause	1903	1904	1905	1906	1907	Totals	1940	1941	1942	1943	1944	Totals
C. V. R.*	1	5	10	5	12	33	117	96	157	139	135	644
Bronchitis			1			1						
Pneumonia *			2		2	4	5	12	12	14	9	52
Tuberculosis			1			1	3		4			7
Grippe					1	1						
Perforated Bowel					1	1						
Bronchial Asthma									1			1
Hernia					1	1						
Pulmonary Abscess							1			1	1	3
Peritonitis									1	1	1	3
Diverticulosis							1					1
Empyema G. B.							1					1
Shock Unspecified									2			2
Toxemia								8	4	2	1	15
Cirrhosis Liver								1	1	1	4	7
Tbc Meningitis									1			1
Empyema Chest								1		1		2
Meningitis Unspecified									1	1		2
Septicemia								1	5	2	1	9
Mesenteric Thrombosis								1				1
Cachexia										1		1
Osteomyelitis								1				1
Alcoholism								1				1
Cavernous Sinus Thrombosis								1				1
Pulmonary Embolism								1	4	5	4	14
Pulmonary Edema								1	3	3	7	14
Femoral Thrombosis								1				1
Acute Pancreatitis								1			1	2
Pulmonary Hemorrhage								1			1	2
Exhaustion									2			2
Hemorrhagic Pancreatitis									1			1
Carcinoma									3			3
AC. Myeloid Leucemia									1			1
Hemorrhage Unspecified									1			1
Sepsis Unspecified									2			2
Shock Post-Operative										2	1	3
Intestinal Obstruction										1		1
Peptic Ulcer Hemorrhage										1		1
Perinephritic Abscess										1		1
Acute Cholecystitis										1		1
Brain Tumor											1	1
Arthritis											2	2
Graves Disease											1	1
Subarachnoid Hemorrhage											1	1
Venous Thrombosis												
Site not Specified									1			1
Total Deaths by Year	1	5	14	5	17	42	128	128	207	177	171	811

* C. V. R. equals cardio-vascular renal disease

* Pneumonia equals lobar and broncho pneumonia

HOME AND HOSPITAL CARE (See Table No. VI)

As a matter of some interest and record, a study was made as to the percentage of cases cared for in final illness at home and in the hospital in the two five

year periods studied. In the early five year period 1903-1907 of the total, 80.74% were treated at home while only 19.25% were treated in the hospital. In the period 1940-1944, 26.82% of the cases were treated at home while 63.18% were hospitalized.

STUDIES OF PRIMARY CAUSES OF DEATH IN INDIVIDUALS WHO HAD DIABETES RECORDED AS A CONTRIBUTORY OR SECONDARY CAUSE OF DEATH (See Table No. VII)

As indicated 42 cases or 22.4% of the total 187 deaths during the period 1903-1907 died of primary causes other than diabetes but diabetes was recorded as a secondary or contributory factor. Of these 42 cases, 33 or 78.57% of the cases died of a cardio-vascular renal disease. Four cases of the 42 cases or 9.52% died of pneumonia while 2.3% each died of bronchitis, tuberculosis, la grippe, perforated bowel, and hernia respectively.

Under the term cardiovascular renal deaths are included such diagnoses as chronic nephritis, cerebral apoplexy, cerebral thrombosis, malignant hypertension, uremia, coronary disease (thrombosis, occlusion), cardiac failure, cardiac decompensation, arterioscler-

osis (generalized or cerebral), acute congestive heart failure, hypertensive heart disease, myocarditis, angina pectoris, acute cardiac dilatation, hypertension, cerebral embolism.

811 or 72.4% of the total 1119 deaths during the period 1940-1944 died of primary causes other than diabetes but diabetes was recorded as a secondary or contributory factor. Of the 811 cases, 644 or 79.40% of the cases died of a cardio-vascular renal death; 52 cases or 6.38% died of pneumonia; other causes are recorded in Table No. VII.

SUMMARY

A comparative study of two five year periods 1903-1907 and 1940-1944 of the deaths from diabetes or where diabetes is recorded on the death certificate is presented as a preliminary study. The entire study of death certificates recording diabetes from 1903 to 1944 inclusive will be published at a later date.

Dysentery, Colitis and Diarrhoea in Japanese Civilian Prison Camps in the Philippines during World War II. III. The Non-Inflammatory, Concurrent and Dual Processes

By

FRANK G. HAUGHWOUT*

NEW YORK, N. Y.

IN THE FIRST TWO PAPERS in this series (1, 2) I have briefly discussed the inflammatory intestinal disorders. We now pass on to the consideration of the non-inflammatory or irritative processes — those disturbances that often are called the "functional diarrhoeas." I have already spoken of the entire group as the diarrhoeal disorders and have further classified them into the dysenteries or inflammatory conditions, and the diarrhoeas or non-inflammatory processes. It remains, therefore, to say just what we mean by the two terms dysentery and diarrhoea since both are diarrhoeal disorders. This is necessary because there is no constant character of either that can be relied upon for differential diagnosis on gross (macroscopical) inspection.

For practical purposes we may say, then, that the difference between dysentery and diarrhoea is that in dysentery the stools are rich in inflammatory products: a stool is not dysenteric unless it contains these. In uncomplicated diarrhoea, there is no inflammatory exudate.

However, let me say in the beginning that stools in diarrhoea are not devoid of cellular matter. Intense non-inflammatory diarrhoeas often are accompanied by a heavy output of tissue cells. The characters of these cells signify that the disturbance is of irritative, not inflammatory origin. They form, with the accompanying mucus, a typical catarrhal reaction in which the cellular moiety is made up of epithelium derived from the intestinal mucosa. Pus is not present unless there is a concurrent infectious process. It is important to remember that in the more severe of these catarrhal reactions, the stool may be blood streaked — even haemorrhagic. It is impossible on gross inspection, to distinguish such stools from the stools of real dysentery, but the distinction is perfectly clear under the microscope. This brings us to another of our fundamental principles or axioms:

9. Diagnosis of the non-inflammatory processes is made by the critical study of the food residue in the faeces, coupled with the study of the response of the bowel wall to an irritative rather than an inflammatory stimulus. There may be marked cellular reaction that is evident in the bowel movements; but this reaction never is inflammatory unless there is concomitant or secondary bacterial involvement. Uncomplicated, it is in the nature of an epithelial transu-

* Late Consultant, U. S. Army Institute of Pathology.

Formerly Professor of Protozoology and Chief, Department of Parasitology, Graduate School of Tropical Medicine and Public Health, University of the Philippines; Chief, Section of Parasitology and Cellular Pathology, Bureau of Science, Manila. (Retired).

date and the cellular reaction, in many instances, is very characteristic.

Mucus is the first response of the intestinal wall to infectious, chemical or mechanical stimulation. It is the matrix within which all the intestinal cell pictures appear. As the polymorphonuclear neutrophile symbolizes the inflammatory reaction of the bowel to infection, so do the epithelial cells of the mucosa symbolize its reaction to conditions of irritation. When the cell picture is epithelial, we have a catarrhal reaction.

The simplest type of catarrhal reaction is seen in the common condition spoken of as gastro-enteritis where the action takes place in the upper tract. In mild cases, relatively few cells appear in the stools, but when the watery diarrhoea is intense, large numbers of epithelial cells are desquamated. Almost invariably they are bile stained. Such changes as are wrought in these cells are largely the result of maceration in the watery medium. There are varying degrees of solution of the chromatin, but for the most part, the nuclei and cytoplasm retain their structure and are easily recognizable. Sometimes, the mucus contains only erythrocytes and a few scattered epithelial cells. On occasion, such a stool may be markedly haemorrhagic. I have shown such a reaction in Fig. 4. of the second paper in this series. The preparation was made from the stool of a patient with a violent putrefactive diarrhoea. We saw many such cases in Santo Tomas Camp. It also is seen, occasionally, in other conditions such as intussusception.

In the more severe and prolonged reactions of the purely chemical, fermentative, putrefactive and fatty diarrhoeas the cellular changes are very marked. In the irritations produced by drugs, the cytoplasm of

the epithelial cells shows hyaline changes and karyolysis is very marked. The cell picture (Fig. 1), of the acute catarrhal response in untoward reactions to hexylresorcinol and drastic purgation, is typical of drug reactions in general. I have seen the bowel react this way to strong solutions of hydrogen peroxide, concentrated solutions of sodium bicarbonate, irritating enemata and a variety of other agents. In severe metallic poisoning, such as that caused by mercuric chloride, there is pronounced submucosal oedema, necrosis of the mucosal epithelium and the formation of a diphtheritic exudate. Bacteria from the lumen of the bowel invade the damaged areas and an acute suppurative condition develops. It forms a picture suggesting that of bacillary dysentery, so much so, that unless the microscopist studies it with the care that he should exercise in the study of every case that comes to him, he may be misled into making a diagnosis of bacillary dysentery. But if he checks his findings, before he commits himself, he will note that endothelial macrophages and evidence of toxic necrosis of cells are absent. His suspicions may be aroused when he notes the healthy appearance of the leucocytes in the exudate which show no cytoplasmic or nuclear degeneration. The history of the case likely will lead to the diagnosis. This condition is not often encountered, but it is well to bear these things in mind, for they usually carry medico-legal significance. I have had that impressed very thoroughly on me on the few occasions when I have run into a case of mercury poisoning.

FERMENTATIVE DIARRHOEAS

The cell picture in the fermentative process is almost as striking, in its own way, as the exudate of bacillary dysentery. In the early stages of a fermentative diarrhoea, the stools are loose, faeculent and contain considerable mucus and gas. They are very acid in reaction. They are conspicuously overloaded with undigested starch. This is the time to check a fermentative diarrhoea by the withdrawal of carbohydrate. If this is not done, the process rapidly increases in severity and may lead to a long and intractable condition. As the condition becomes acute, large quantities of mucus appear and soon the columnar epithelium begins to flake off the colonic mucosa. At first the cells retain their normal contour and cytoplasm and nuclei are relatively intact; but as oedema of the bowel wall increases, the cells become swollen and hydropic. The cytoplasm takes on a spongy appearance and nuclei become pyknotic. By this time, the cells are being cast off from the mucosa in immense numbers and it is evident that extreme irritation is present. This irritation doubtless is caused by the products of carbohydrate fermentation — gases and organic acids. Probably the most potent of the latter is butyric acid which is so abundant in these cases that the stool is permeated with its odor. The result is a pure catarrhal reaction consisting solely of hydropic epithelium and mucus (Fig. 2) and, in the more intense accesses, variable amounts of blood. Unless there is a concurrent inflammatory

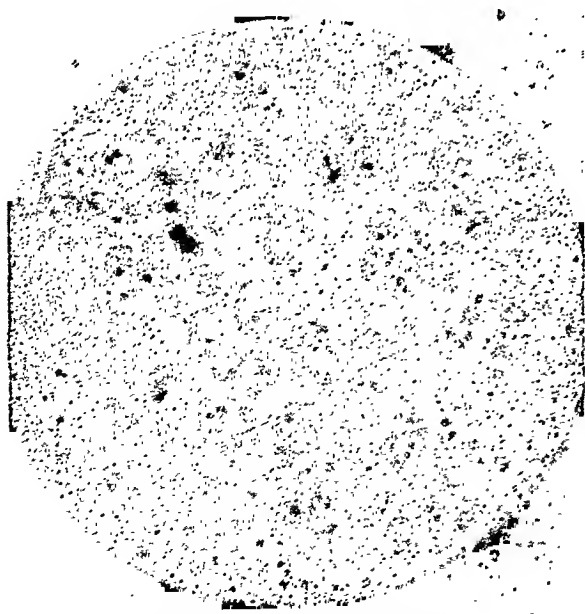


Figure 1. — Cell reaction following administration of hexylresorcinol and purgative. Note extreme karyolysis in epithelial cells and absence of leucocytes.

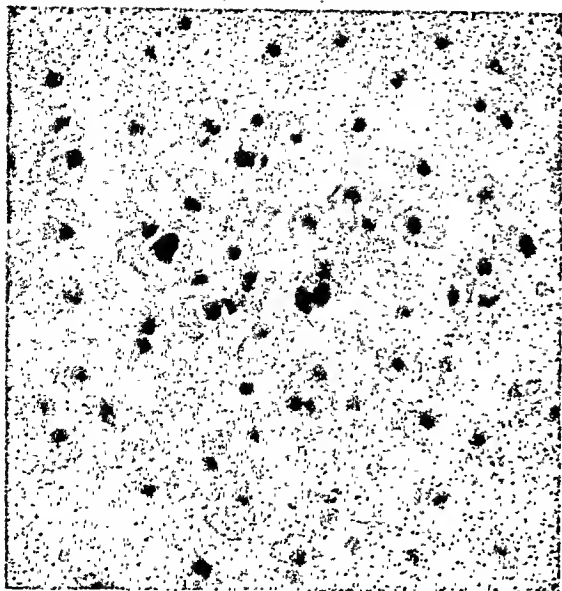


Figure 2. — Hydropic epithelial cell reaction in exfoliative catarrh. Note absence of leucocytes.
Army Institute of Pathology, Neg. No. 90589.

process, no pus is present and there is neither toxic necrosis of cells nor endothelial reaction. Particularly, if blood is present, the gross appearance of the stool suggests dysentery, but the nature of the process is perfectly clear under the microscope. For want of a better term, I have styled this stage of fermentative diarrhoea, Exfoliative Catarrh.

In a number of instances in the camps, this exfoliative catarrh developed in patients who already had a chronic colitis. The alteration in the picture is not difficult to analyze and should lead to no serious confusion in the mind of the microscopist (Fig. 3). The hydropic epithelial cells with their pyknotic nuclei are there and if the complicating process is a chronic colitis the leucocytes will be normal in appearance. If the complication should be one with bacillary dysentery, the typical stigmata of the bacillary exudate will appear. In acute amoebiasis, trophozoites of *Endamoeba histolytica* will make their appearance. In Santo Tomas Camp, I encountered one patient in whom both bacillary and amoebic dysentery were combined with a case of exfoliative catarrh, the three being simultaneously active. This sounds complicated, but such a picture can be interpreted with ease by a careful and experienced microscopist who can then tell his clinical confrere exactly what he is up against and why the patient does not wholly respond to treatment directed against just one of those three conditions. This is an excellent, even though extreme, example of what I meant when I spoke of the interlocking activities of bowel disorders as a group.

Unless the process can immediately be checked by the method I have given, these fermentative diarrhoeas may present a grave problem. The fermentative diarrhoeas in the prison camps gave us far more trouble than the dysenteries and I think, in the long run, they

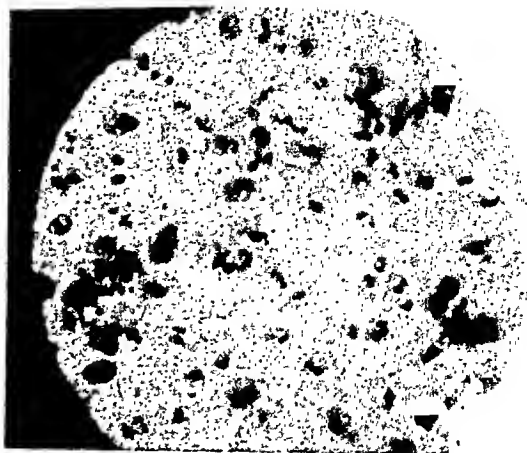


Figure 3. — Exfoliative catarrh complicating chronic colitis. Note that pus cells, scattered among the hydropic epithelial cells, show no signs of toxic necrosis.

were harder on the patients. The thing we most dreaded was the extension of the fermentative process into the small intestine. Once it got above the ileo-caecal valve it might extend even to the duodenum and then, with the means at our disposal, we were powerless to stop it.

One very important factor underlaid these fermentative diarrhoeas in the prison camps: the inmates of the camps were universally meat and wheat eaters and physiologically not adapted to a diet, the main item of which was rice. Their amylolytic enzymes were not equal to the digestion and assimilation of the unaccustomed amount of carbohydrate they were forced to eat. Such a diet has no bad effects on Chinese, Japanese, Filipinos and other eastern races, for their digestive apparatus has become adapted to it through many centuries of such diet. The reaction to this high carbohydrate diet among the prisoners in the Baguio camps was immediate. By February 1942, there were many cases of fermentative diarrhoea and large numbers of these patients early developed exfoliative catarrh.*

Unfortunately, these fermentative diarrhoeas began just about the time the first outbreak of bacillary dysentery in Baguio began to subside and it was very difficult to convince some of the physicians in the camp that they were not dysentery. The stools were mucoid, the mucus was cloudy and obviously carried a high cell content. Many of them were blood streaked. But with all that, the nature of the disturbance was perfectly clear under the microscope. As might be

* Since this paper was written, I have seen an editorial comment in this Journal (7) that is exceedingly apropos of what I have said in this paragraph. It may be read with great profit by those who are interested in the factors underlying our fermentative diarrhoeas. I have the feeling that our observations on these disturbances, contribute an interesting illustration to the proposition advanced by the writer of the editorial. We have given a very striking example of what may happen when a people run counter to "racial wisdom in food selection."

expected, these patients did not respond to anti-dysenteric treatment.

That the real nature of this diarrhoea might be made clear, a volunteer was submitted to a diet consisting solely of rice and water. By the end of the first week his stools were laden with undigested starch and fermentation was active with extreme abdominal distention. By the third week he had developed a most acute exfoliative catarrh. His stools had, meanwhile, been demonstrated and most of the men were beginning to be convinced. However, there still were some Doubting Thomases, so the volunteer was fed mucus from a new case of bacillary dysentery. He promptly came down with dysentery and the bacillary exudate became superimposed upon the catarrhal reaction which all could see. This clinched the argument. From then on, the condition was accepted by all hands.

Subsequent developments in this volunteer are of interest. The fermentative process persists to this day (the patient is still under observation) and at times has been very acute. At one time, when bowel distention was extreme in the camp, a loop of bowel was forced through a hernia and complete obstruction ensued. At operation the strangulation was reduced, but in the process the intestine was cut and the peritoneum became infected. Peritonitis and then ileus ensued. The volunteer was seventy years old and a poor subject for such an experience, but under heroic treatment he survived. A faecal fistula drained for eighteen weeks before it closed. He has sustained eight recurrences of his dysentery and the fermentation is still active in his small as well as in his large intestine. His weight fell from 168 to 92 pounds, but he is now back to about 140 pounds. He can tolerate very little carbohydrate in his diet. His present condition may be regarded as typical of the condition of many survivors of the prison camps.

These fermentative diarrhoeas afforded an excellent opportunity to study the development of "mucous colitis." Many of the more severe cases of exfoliative catarrh developed this. It first becomes apparent when the mucus of the exfoliative catarrh begins to lose its hyaline character and become inspissated. The end result of this is the passage of typical mucous casts of the bowel. I have described this process in some detail elsewhere (3). I mention it here because of the light it throws on the development of "mucous colitis," and how at least one type of it may arise.

The bowel distention caused by these fermentative conditions always is uncomfortable to the patient and in the camps it threw confusion into the surgical clinics. In a large number of instances, this discomfort amounted to real pain that centered in the right lower quadrant. This pain was increased on pressure and there was definite tenderness and rigidity over the appendiceal region. This, of course, suggested appendicitis. There was, however, no rise of temperature, neither was there any leucocytosis. Nevertheless,

numerous appendectomies were performed on patients with an acute fermentative diarrhoea, with the delivery of appendices in which no inflammatory changes could be detected. Some of these appendices were distended with gas when they were delivered to me and this gas escaped with a faint hiss when the organ was incised. The situation was particularly trying to the surgeons because many of the patients were rather poor subjects for operation. It was further complicated by the fact that occasionally a case of genuine appendicitis would develop. Several hernias strangulated as a result of distention and other perplexing surgical problems arose from time to time from the same cause.

One case, in particular, deserves mention because it was so typical. The patient was a girl about three years old who had been suffering from a severe fermentative diarrhoea for several weeks. One afternoon she developed severe pain over the appendix. My associate, Dr. Allen, was called and she in turn sent for me. We were skeptical regarding the existence of appendicitis, especially as the child's temperature was normal. Study of the blood yielded a total leucocyte count of 6,200 with 52% neutrophils. We decided to wait and see what a later blood count would show. While we were waiting, the child asked to be put on her "pottle." She passed a copious stool accompanied by heavy flatus and immediately fell over in a faint. When she came out of this the abdominal pain had subsided and there was only moderate tenderness over the appendix. Within an hour all pain and tenderness had ceased. The next morning she was out and playing as usual with the other children.

One of the most annoying symptoms of which our patients with fermentative diarrhoea complained, was frequent micturation at night. Many of them had to arise several times during the night to empty the bladder. This was frightening to some who feared they had come down with "kidney disease." After some experimental work, however, it was determined that this was caused by intestinal distention of such an extreme degree that the capacity of the urinary bladder was reduced by the pressure upon it.

Fermentative diarrhoeas are more fully covered in other publications (3, 4) to which the reader is referred. I am summarizing the general symptomatology as observed by us in Table I.

The treatment of these fermentative conditions offered great difficulties which would have to be experienced before they could be appreciated. Obviously, they were caused by the ingestion of more carbohydrate than could be disposed of by the persons affected. It was equally obvious that the only way the problem could be met was by removing the cause. This would be simple enough under peace time conditions when food substitutes were available; but in the camps the main stay of the diet was rice. The interdiction of this, of course, was impracticable. The only remedy we had was to reduce the rice to an amount that could be digested by the patient. Few people took kindly to this idea and we had a rather pathetic struggle with the children and their mothers. We finally succeeded in demonstrating that the condition could be brought under control by reducing the rice intake to an amount that could be digested. It was pointed out that rice

TABLE I

Symptomatology of Carbohydrate Intolerance

Early Stage	Stools loose, acid, light in color, odorless, and laden with undigested starch.
	Gaseous distention with marked abdominal discomfort.
	Excessive flatus — odorless.
	Nocturnal colonic distress, disturbed sleep, excessive salivation.
	Nocturnal polyuria.
Late Stage	Increasing frequency of henteric to pultaceous stools becoming very mucoid.
	Occasionally, constipation.
	Persistence, sometimes exaggeration of early symptoms.
	Stools diarrhoeal with penetrating butyric odor; very mucoid with heavy epithelial content; blood occasionally present. The stage of exfoliative catarrh.
	Extension of fermentation to small intestine.
Late Stage	Abdominal pain and tenderness, often focusing in the caecal region.
	Pain and rigidity over the appendix. Simulation of other surgical intra-abdominal conditions.
	Protrusion of abdominal herniae; sometimes strangulation.
	Frequently late development of "mucous colitis" with passage of bowel casts of inspissated mucus.

taken in quantity exceeding this determined amount not only passed through the alimentary tract without contributing to the nutrition of the eater, but underwent fermentation when it reached the colon and gave rise to the diarrhoea.

This entailed an enormous amount of microscopic work. Each day the individual rice rations of the affected were cut down a little. The stools of every patient were studied daily until, after successive reductions of rice, it was found that only a small amount of undigested starch appeared in the faeces. The volume intake was fixed at that point. As it varied between individuals, some care was necessary in the appraisal. In Baguio, values on the volume of the diet were not accessible to us, but these were available in Santo Tomas in 1944, from figures compiled by Miss Elvessa Stewart, the camp dietician. I am showing (Chart A) the correlation between rice intake and the incidence of fermentative diarrhoeas between February and December 1944, during which time the prisoners were on starvation rations. In the graph the average daily per capita ration of rice in grams for each month is shown in Curve 1. Curve 2 shows the monthly admissions to our clinic for fermentative diarrhoea. The parallelism of the curves is striking and it will be seen that the incidence of fermentative diarrhoea declined in concert with the reduction of the rice ration so that fermentative diarrhoeas automatically ceased to be a problem after August — the prisoners were able to digest all of the small amount of rice the Japanese doled out to them.

FATTY DIARRHOEAS

Many of the patients who reported to our clinic

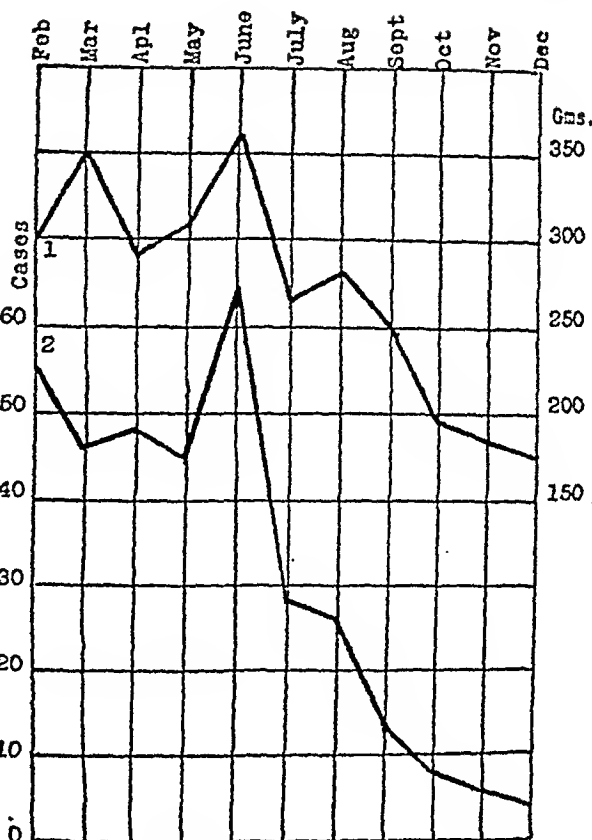


Chart A. — Correlation between the daily rice ration in grams (Curve 1) and the incidence of fermentative diarrhoea (Curve 2). Note how the diarrhoeas declined as the rice ration fell.

showed evidence of impaired fat splitting before the end of the first year of imprisonment. I have no explanation to offer for this and simply cite it as a factor that may have influenced subsequent events. Disturbances of fat metabolism in the camps brought out the interesting point that fatty diarrhoeas may run an epidemic course and that it is possible to determine their cause by microscopical methods, and control them by eliminating that cause.

The interpretation of steatorrhoeas or fatty diarrhoeas often is a matter of some difficulty and mistakes are frequently made. I have seen transient fatty diarrhoeas diagnosed as sprue and long and expensive treatment carried out that could have been obviated by a correct diagnosis and the application of relatively simple dietetic measures in the beginning. Some years ago I summarized my findings on a number of these cases (5) and also pointed out the probable existence of a pre-sprue condition that is amenable to treatment if discovered. We had very few cases of sprue in the camps and I think that all of them had developed before the war. It is impossible here to go into details and fallacies connected with the fatty diarrhoeas, but I have discussed them broadly elsewhere (3). I shall content myself with an account of the fatty diarrhoeas encountered in the camps.

Our most satisfactory observations were made in

Santo Tomas Camp during the last year of imprisonment. At no time during that year did the daily per capita fat ration exceed 20 grams; it averaged 13 grams daily for the year. As has been said, it was early apparent that something had intervened to inhibit fat digestion. What that was did not become clear. Whether "atrophy from disuse" might explain it, I cannot say. The fact remains that when a sudden stress was placed on fat splitting we had trouble.

This was first noted in December 1943, when Red Cross kits arrived in the camp. These kits contained powdered milk, chocolate, oleomargarine and canned corned beef. The number of fatty diarrhoeas showed a definite upward trend forthwith. During March 1944, this rise became marked and by April it was evident that some definite food factor was involved. The fatty diarrhoeas were then restricted mainly to the young children. Their loose stools were heavily laden with unsplit fat and much of their other food was being carried through in an incomplete state of digestion by ensuing diarrhoea with resulting nutritional loss all around. The camp, in general, regarded this as a sudden influx of dysentery, but the microscopical evidence to the contrary was perfectly clear.

An investigation disclosed that quantities of milk of the carabao (water buffalo) were being smuggled into the camp and given to the children to replace the cow's milk which was unobtainable. The fat content of carabao milk is much higher than that of cow's milk and the children were unable to split it. It was a sad business to meet this situation. The fat, itself, seemed not particularly irritating, but it loosened the stools and the diarrhoea robbed the children of much of their slender allowance of other foods. It was evident they derived little nourishment from the milk. Then ensued another battle with children and parents, but in the end they were convinced by the evidence and the use of carabao milk was discontinued. The diarrhoeas immediately ceased.

Shortly before this, however, there began a sharp rise in the fatty diarrhoeas among the adults, which could not be traced to the carabao milk. These new fatty diarrhoeas often were very acute and accompanied by abdominal cramps that sometimes were very severe. In the more severe of them there was heavy production of mucus and desquamation of intestinal epithelium. The stools were literally saturated with neutral fat. Again ensued the question of dysentery which was once more promptly disposed of.

Microscopical study of the stools quickly gave a clue to the cause of the disturbance. The stools were found to contain large numbers of spherical to oval capsules of about the size of a hookworm ovum. Sudan (III) showed these capsules to contain neutral fat. A study of the food in the official camp dietary failed to discover similar bodies and another investigation was made. This disclosed that quantities of the fruit avocado were being brought into the camp. Study of the pulp of the avocados showed them to contain fat bodies identical with those found in the faeces. The internee who had been the subject of the

rice experiments in Baguio, submitted himself to an exclusive diet of avocados for several days. His intestine, already in a state of extreme irritation, promptly reacted. His stools became saturated with neutral fat and contained innumerable avocado fat bodies. He suffered severe abdominal cramps and became prostrated. This convinced us of the cause of the trouble.

This was a severe blow to the internees who were deriving great comfort from the avocados and it was difficult to induce them to give them up. Many were persuaded to submit the case to trial and in this way most of them became convinced. They found that on discontinuing the eating of avocados, the diarrhoea ceased within a few days, but immediately recurred if they ate avocados again. However, it was not until the latter part of July 1944, when the supply of avocados was cut off, that the "epidemic" ceased. After that, the incidence of fatty diarrhoea fell almost to zero.

The fat content of the Philippine avocado is about 17%. There appears to be a very irritant principle in the oil — one far more irritant than that of castor oil. The effects are cumulative and the symptoms persist until the intestinal tract has become clear of the oil. Some persons are more sensitive to this oil than others. We formed the impression that the state of chronic intestinal irritation in the camp had much to do with the incidence of avocado diarrhoea. Under normal intestinal conditions most persons seem able to eat avocado with impunity.

Recently I was asked to study an outbreak of "seasonal colitis" in California. I was able to study the cases of about twenty persons who gave a long history of periodic diarrhoea and abdominal cramps and had been under treatment for chronic colitis. Avocado fat bodies were found in nearly all of these during exacerbations of the disorder. Interdiction of the fruit resulted in the disappearance of the symptoms. Those who tested the validity of the diagnosis by resuming consumption of the fruit were convinced when the diarrhoea relapsed. It seems improbable that avocado diarrhoea is a real problem in gastroenterology in this country, but it may furnish the solution of some periodic diarrhoeas that are resistant to colitis treatment. The diagnosis is simple under the microscope and is easily checked clinically.

Just before the camp was freed in February 1945, another fatty diarrhoea started. This was found to be caused by rancid soya bean cake. We were rescued before a thorough study could be made of this outbreak.

PUTREFACTIVE DIARRHOEAS

Notwithstanding the daily per capita protein ration at Santo Tomas for the period extending from February to December 1944 averaged only 31.2 grams, which is only 44% of what it should have been, putrefactive diarrhoeas were exceedingly common in the camp. As a matter of fact, they also were common in the

Bagnio camp by the middle of the first year. They gave us a lot of trouble for it takes a lot of staying power on the part of patient and physician to see a thoroughly established putrefactive diarrhoea through to what the playwrights call a happy ending. Of the more severe cases many develop a marked steatorrhoea. Others blend into an intense catarrhal enterocolitis which may be accompanied by haemorrhages; they are less frequent than the steatorrhoea.

Terminal steatorrhoea in a putrefactive diarrhoea has been recorded by many observers and there seems to be a general impression that the liver is involved. We regarded them as the result of absorption of toxins from the bowel that disturbed hepatic function. The fats in the stools were predominantly combined fatty acids (soaps) and the faeces and urine contained excessive amounts of hydrobilirubin. Definitely, the absorption of fats was inhibited. The catarrhal enterocolitis developed only in extremely intense and prolonged putrefactive diarrhoeas and appeared after most of the active putrefaction had subsided. For that reason, it is difficult to fix upon the cause of this condition unless the history of the case is known. It is a very acute condition. The mucoid stools are heavily bile stained and contain considerable epithelium but no pus. Haemorrhages may be so profuse as to be alarming.

We found it convenient to classify our putrefactive diarrhoeas into two groups: In one of these, they are frankly putrefactive from the beginning; many of them are gastrogenous. A variety of causes may be found in the second group. Intestinal allergy frequently merges into a putrefactive diarrhoea. The food intoxications are very prone to do this. A simple gastroenteritis may develop into a putrefactive diarrhoea. Moreover, it is well to investigate cases of "intestinal influenza" for I have found that sometimes when a clinical diagnosis of intestinal influenza has been made the diarrhoea is definitely putrefactive and subsides on a protein free diet. I do not assert that all cases of intestinal influenza can be resolved to putrefactive diarrhoea on microscopical evidence but I do suggest the study of the stools in such cases where the clinical history is at all uncertain.

Most putrefactive diarrhoeas will relapse at the drop of the hat. In the camps we found that interdiction of proteins and alkalies usually brought about abatement of the symptoms in a short time. However, considerable time should be allowed to elapse before the eating of proteins is resumed. The diarrhoea may quickly cease and the stools appear normal, but that does not mean that proteins may be taken at once. They should be cautiously added to the diet in about two weeks and it is well to start with vegetable proteins. Eggs and beef will almost invariably precipitate a relapse if they are given too soon.

The diagnosis of putrefactive diarrhoea calls for considerable care. I have treated the matter fully in another publication (3). The study should be started by eliminating dysentery and the fermentative and

fatty diarrhoeas. Stools containing marked amounts of meat fibre, either wholly or partially undigested, form an excellent culture medium for putrefactive organisms and, hence, are suspicious. An odor of hydrogen sulphide is good evidence when contrasted with the odorless stools in fermentative conditions. It cannot be confused with the odor of butyric acid in the latter. If one realizes the limitations of the Obermayer reaction, one may place some stress on the presence of indicanuria. Lastly, it must be pointed out that the stools in putrefaction are strongly alkaline as contrasted with the strongly acid stools of fermentative and some fatty diarrhoeas. One can build up a pretty good case on such evidence. While, in principle, I have an aversion to the therapeutic diagnosis yet, the proof of the pudding not infrequently lies in the eating. Regrettably, the therapeutic diagnosis too often is the resort of the man who either is mentally lazy or is not sure of himself. It can work great harm. However, employed as a check on a diagnosis already fairly established, it may be useful. If, after consideration of evidence such as has been outlined above, protein and alkalies are withdrawn and the diarrhoea abates, and then, if the patient eats some protein, and it immediately relapses, one may feel he is on the right track. That is the method of diagnosis and treatment we followed in the camps. We found the administration of dilute hydrochloric acid in adequate dosage very helpful in most cases. At times, the supply of salt was withdrawn by the Japanese and we observed that this invariably was followed by a rise in the incidence of putrefactive diarrhoea.

The basic protein diet allowed by the Japanese was moderately supplemented from time to time, from other sources. Each time that happened a new crop of putrefactive diarrhoeas developed. To illustrate: The Red Cross food kits, before mentioned, were distributed in December 1943. The internees immediately became divided into two groups: those who could not resist the temptation to dip freely into the kits and enjoy themselves while the food lasted, and those who prudently determined to make the supply of canned meats last as long as possible. Both groups got into trouble. Those in the first group gorged themselves with meat the first few days and many became violently ill. It may be said that in spite of this they did the same thing when food arrived after liberation of the camp, with the same results.

The other group saved their canned meat until April, at which time the regular camp ration had fallen below 1400 calories and starvation was setting in. They then began to open their hoarded cans of meat. But they were still prudent. They did not eat it all at once; they string the consumption out for several days, stowing the unconsumed residue away each day in a trunk or bag or, in some instances, under the bed pad. The result that might be expected came to pass in the form of an outbreak of food intoxications nearly every one of which developed into a putrefactive diarrhoea as soon as the acute symptoms subsided. These cases string along until June notwithstanding our

campaign against the eating of left-overs. By the end of June practically all the Red Cross food had been consumed. There was a lull in the incidence of putrefactive diarrhoeas for about two months. Milk, meat and eggs were then totally absent from the diet and the only protein the prisoners had was the scant amount of vegetable protein in the regular camp ration.

The putrefactive incidence began to rise again about the first of August. It was, as usual, ushered in by an outbreak of food intoxications that were traced to fish imported into the camp by the Japanese. These fish were putrid when we received them. They were served without being either degutted or degilled, but the starving prisoners ate them notwithstanding their foul odor. They were, by that time, supplementing their diet with dogs and rats that abounded in the camp, as well as the leaves of trees, and the grass that grew in clumps on the arid grounds. Some even went so far, in their famished condition, as to eat garbage salvaged from the swill pails outside the Japanese guard house. If the reader will reflect upon these conditions, he may be able to account for the intestinal conditions that pervaded the camp and of the enormity of the task that was presented to us in dealing with the situation. The etiology of "jail diarrhoea" will become clear to him. It probably is an understatement when I say that 60% of the camp inmates suffered from acute intestinal disturbances of one kind or another. It was rendered particularly distressing by reason of the fact that the water closet facilities were inadequate to deal with the situation. Intestinal incontinence was common and accidents were frequent among the internees who often had to stand in line for an hour or more before they got their turn at the toilet seat. The problem of keeping the latrines clean was well nigh insoluble and with the swarms of flies in the latrines, that later settled on the food at meal time, it is not surprising that bacillary dysentery was constantly endemic in the camp.

There was some mitigation of these conditions when the stale fish were finally banned from the diet. Also, the rice ration had by then been reduced to the point where relatively few internees were developing fermentative diarrhoea. Fewer new cases of either type of diarrhoea developed but a high proportion of those who had been affected developed intense secondary catarrhal conditions which we were powerless to substantially ameliorate. The ingestion of leaves and grasses, many of which contained irritant or mildly toxic substances must have increased the irritation. This uncontrollable situation then became one of almost purely scientific purpose and we studied it as thoroughly as conditions would let us, while doing all we could for our wretched patients. Meanwhile the ration was rapidly falling to its low of between 600 and 700 calories per capita per day.

If the reader will look back to what I have written in my first paper (1) he will see what I meant when I said we had defined the nature of "jail diarrhoea." He also will realize the potentialities of the interlocking activities of all these dysenteries and diarrhoeas. Per-

haps he will see how these things can enter into the problems of routine peace time medical practice in this country if only he will look for them.

In illustration of this, let me cite a condition we frequently encountered among our patients. It seems too anomalous to be true, but we often saw patients in whom fermentative and putrefactive conditions were active at the same time. The putrefactives seemed to center in the upper intestine and the fermentatives in the colon. The only treatment available to us consisted in the withdrawal of the food, that at the time, seemed to be causing the trouble — proteins in the case of the putrefactives and carbohydrates in the fermentatives.

However, we found we had to be careful and keep these cases under constant microscopical supervision. If we originally spotted a case as putrefactive and pushed carbohydrates, we might be surprised to see the case suddenly become fermentative. Or, again, if the case was fermentative and we reduced the carbohydrates beyond a certain point our diarrhoea became putrefactive. These changes often were very abrupt, literally taking place overnight. It was interesting but appalling and the problem was not mitigated by the difficulty presented by some patients who could not understand why we so radically changed the dietary regime. To them, it looked like vacillation on our part and we could well understand why their confidence in us faltered. However, it was the only means we had for gaining any control over the situation. Had it not been for the revelations of the microscope we would have been utterly at sea in these cases. But for the clues we thereby gained many of these patients would have died — from sheer exhaustion and loss of nourishment if nothing else.

DUAL PROCESSES

We have so far discussed the phenomena connected with the infectious, inflammatory processes and those arising from non-inflammatory or irritative sources. Let us now bring our story to a close by citing two of the conditions in which there appears to be an essential collaboration between inflammatory and irritative stimuli. I refer to intestinal allergy and salmonella dysentery.

The stools of acute intestinal allergy, in the gross, so closely resemble the stools of bacillary dysentery, and the physical symptoms so often are urgent, it is important that an accurate differential diagnosis be made at once. Fortunately, the cellular picture presented by intestinal allergy is well defined and the microscopist will have no trouble in making a quick diagnosis either way. It simply is a matter of securing the material early in the attack.

The first impression the microscopist is likely to gain on examining a preparation made from the stool of a case of intestinal allergy is that he has a case of bacillary dysentery. There is a massive leucocytic exudate and many large cells are present that he may regard as macrophages on a hasty examination. He

also will note that the leucocytes contain granules that superficially resemble the fat globules seen in leucocytes in bacillary dysentery. If he is alert, however, he will see that the large cells are epithelial — not endothelial, and he also will perceive that the granules or droplets in the leucocytes are smaller and more uniform in size than the fatty inclusions in the leucocytes of bacillary dysentery. They do not stain with Sudan III. If he stains a preparation in haematoxylin and eosin, which he can do in a few minutes, he quickly recognizes the large cells as epithelium and the cell granules as eosinophilic — not fatty. In other words, he has an exudate made up of eosinophiles and epithelium instead of one composed of neutrophils and macrophages. The picture is perfectly clear.

I am showing (Fig. 4) two fields from the same preparation, made from a case of acute intestinal allergy. They have been photographed at high magnification so that the cell granules will be distinctly visible. Study of these two pictures should make it clear that the reaction here is dual and that there is distinct segregation of the two elements. In the upper figure (Fig. 4 A) nothing appears but hydropic epithelial cells which one should compare with the cells in exfoliative catarrh (Fig. 2). Obviously they are the response of the mucosa to an irritative stimulus as was the case

in exfoliative catarrh. In the other figure (Fig. 4 B) the response will be seen to be almost wholly eosinophilic, but one can discern a few neutrophils in the field. The eosinophiles contribute about 60% of the leucocytes in the allergic exudate. A small number of neutrophils always is present, but the exudate can hardly be regarded as inflammatory in the degree that the bacillary exudate is inflammatory. No doubt ever should arise.

This cellular picture persists as long as the acute physical symptoms are present; but it fades rapidly when these are gone. The epithelial cells are the first to disappear, then the neutrophils and at the end of 24 to 36 hours, only a few eosinophiles remain. These are in a bad state of degeneration and at the end the only way they can be detected is by the presence of scattered clumps of eosinophilic granules which, if the case has been seen late, justify the microscopist in saying that the attack probably has been allergic. This may give the clinician something to work on as against future attacks. So much for our criteria on intestinal allergy. I have cited cases in another publication (6).

In considering the matter of *Salmonella* infections we must reckon the double role played by that organism in causing food intoxication and also as a cause of dysentery of the bacillary type. As we have seen,

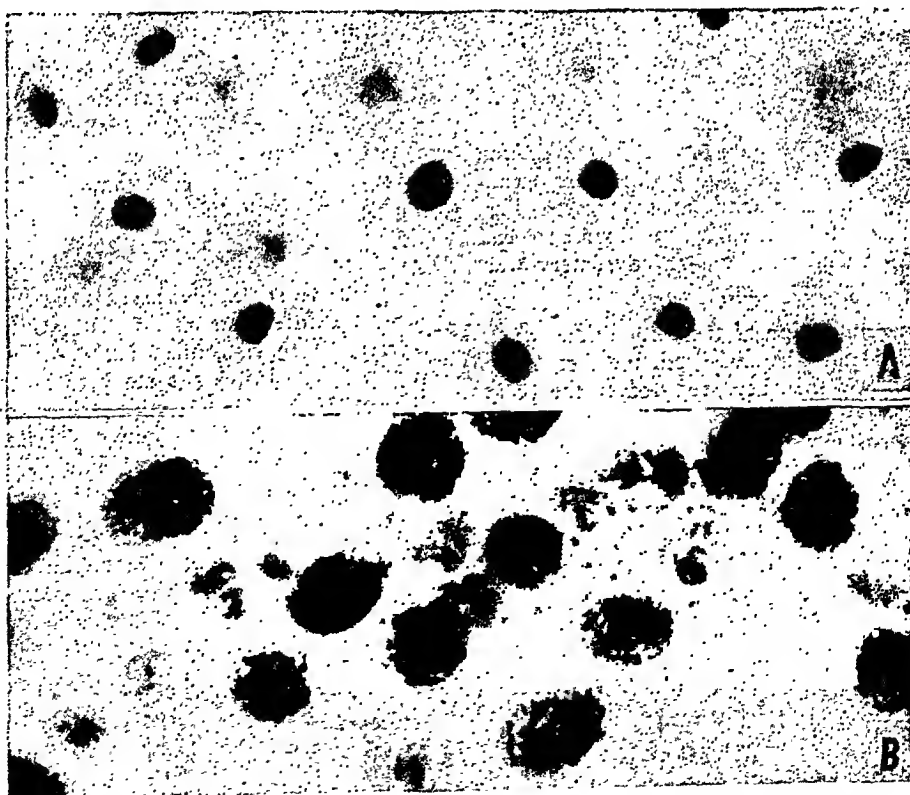


Figure 4. — Dual reaction in intestinal allergy as shown in two fields in same preparation. The reaction from the mucosa (A) is seen to be purely epithelial; compare with Fig. 3. The exudate (B) is composed mainly of eosinophiles, but a few neutrophils are present. Numerous eosinophilic granules from ruptured cells are seen in the background. Army Institute of Pathology, Neg. Nos. 41133 and 41175.

chemical stimuli, which include the reactions of the intestine to the irritants produced in intoxication, yield an epithelial reaction and infectious processes yield a characteristic inflammatory reaction. So far as my studies have gone it is indicated that *Salmonella* may give rise to either or both of these types of reaction. When we have both, we have salmonella dysentery.

I put this proposition out tentatively without prejudice to what further study may disclose. Several years ago in China I made a study of the cellular reactions produced by *Salmonella*. I had the collaboration of Dr. A. A. Lempert of Shanghai who did the bacteriological work. I brought my preparations and notes back to the Philippines in the fall of 1941. They were stolen by the Japanese when they occupied Manila in 1942. Hence, to illustrate my remarks I am forced to fall back on material I have obtained in this country since my repatriation.

The case I am citing (Fig. 5) was studied by courtesy of Dr. Ernst Friedlander of San Jose, California.

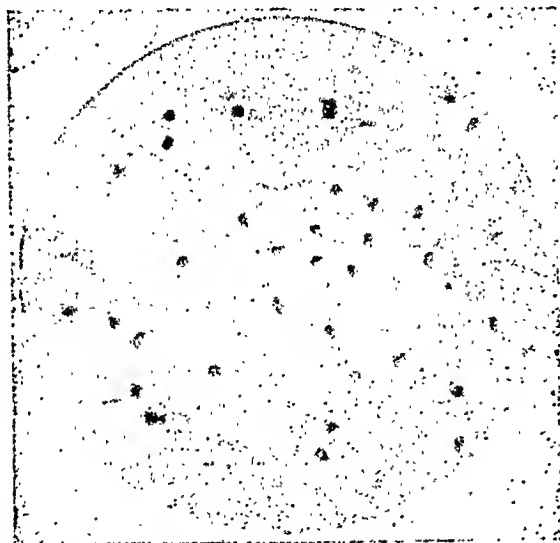


Figure 5. — Exudate of a case of dysentery from the stool of which *Salmonella schottmuelleri* was isolated. The cell at the right middle margin probably is a necrotic macrophage. The other large cells are hydropic epithelium; compare with Fig. 3. Note that the neutrophils are young forms.

The bacteriological work was done by a thoroughly competent bacteriologist in the city health laboratory. He reported the isolation of *Salmonella schottmuelleri*, from the stool of the patient.

These salmonella dysenteries yield an exudate that is definitely of the bacillary type, but it shows some departures from the *Shigella* exudate. The background of the *Salmonella* exudate, like that of *Shigella*, is the neutrophilic leucocyte, but I have noted in several instances that the leucocytes were mostly young forms with two nuclear lobes. Such was the condition in this case, as can be seen in the figure. There is some fatty degeneration of leucocytes and evidence of toxic cell necrosis which is most conspicuously seen in the oval cell at the right mid-margin. Endothelial macrophages

may be found in all cases, but they are not so numerous as they are in *Shigella* cases. The necrotic cell mentioned, probably was a macrophage, but of that I am not quite certain. The *Salmonella* picture is completed by the large hydropic epithelial cells around the margin of the figure and at the top center. The cytological picture may be said to be in harmony with the clinical manifestations of this type of bacillary dysentery. I did not include it in my account of bacillary dysentery, because I wanted first to show the characters of the irritative responses. It would then be clear that *Salmonella* exudates were the expression of combined inflammatory and irritative reactions. In intense intoxications caused by *Salmonella*, the cell reaction is purely epithelial.

These *Salmonella* exudates should be further studied in collaboration with a bacteriologist experienced in the study of this organism. I have studied relatively few cases in which I was able to enlist the help of a bacteriologist who had the specialized knowledge of *Salmonella* that I felt justified complete confidence on my part in the association between the organism he recovered in culture and the exudate from the same case that was studied by me. Accordingly, I put this picture out only tentatively although I believe subsequent research will confirm it.

I may add that many cases of intestinal allergy were detected in the camps, particularly at times when we were experiencing an outbreak of putrefactive diarrhoea. In an outbreak of food intoxication that affected about 50% of the camp population in Baguio, I picked up about a dozen cases of allergy. This outbreak was caused by the eating of putrid carabao meat that had been brought into the camp as a "treat" by the Japanese, the camp having been practically without meat for some weeks.

Strangely, however, with all the cases of food poisoning which probably were caused by organisms of the *Salmonella* group, we did not detect any cases of dysentery that we felt certain had been caused by *Salmonella*. All exudates were definitely of the *Shigella* type.

This concludes our little excursion into the fields of dysentery, colitis and diarrhoea which we have examined from the viewpoints particularly, of diagnosis and management. I shall bring it to an end by stating the final, but not the least important, of our ten fundamental principles or axioms:

10. The association between the microscopist and the clinician always should be close and replete with mutual confidence. It should be as collaborative as that between the surgeon and the anaesthetist. In the greater number of instances, the task of final diagnosis falls upon the microscopist. He usually must also furnish the explanation of any change in symptomatology, whether it lies in an intensification of the primary process or the super-vention of another condition that may require a separate course of treatment. The clinician is in the best position to observe any changes in the physical reactions of the patient and he should seek an explanation of them from the microscopist. The microscopist, on his part,

in his daily studies of the patient's stool, may detect early changes in the pathological picture before there is a physical response to them by the patient. He should then immediately place the physician on his guard. In this way recurrence, or the development of a com-

plication that may be difficult to control, may be checked. The clinician also may render signal aid to the microscopist by informing him of extra-intestinal factors that may modify the interpretation of the microscopical picture.

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Abstracts Of Current Literature

ABSTRACT EDITOR — M. H. F. FRIEDMAN

Jefferson Medical College

1025 Walnut Street

Philadelphia, Pennsylvania

METABOLISM & NUTRITION

ALDRICH, R. A. AND NELSON, E. N.: *Megaloblastic anemia in infants*. (*Journal-Lancet*, Nov. 1947, V. CXVII, No. 11, 399-402).

Six cases were encountered in infants in a few months, satisfying the diagnostic criteria laid down recently by Zuelzer and Ogden for "megaloblastic anemia in infants" which so closely resembles pernicious anemia in its smear picture, and which, for decades has been erroneously regarded by clinicians as pernicious anemia or has gone unclassified. Bone marrow examination is important in the examination. Cure is obtained (without later relapse) through the use of purified liver extract or folic acid. The six cases reviewed had been on an exclusive dietary of synthetic milk, while developing the disease.

BORELL, U.: *Studies on the function of the pineal body with the aid of radioactive phosphorus*. (*Nordisk Med.*, Oct. 24, 1947, V. 36, No. 43, 2138-2141).

In the cells of the pineal body there is a vigorous

metabolism of the phosphorylated intermediate links which appear in the carbohydrate cycle. These links contain much energy. A less lively metabolism is noted in some of the protein fractions. The pineal has the lowest metabolism during the infantile period. In the fertile age of the rats the phosphorus turnover remains at a constant high level and increases somewhat during senility. After castration an increased activity was obtained in the pineal body and the increase was more pronounced in females. After pinealectomy the phosphate metabolism decreased in the ovaries and uterus and increased in the testis. Experiments are being carried out to study the further connection between the pineal body and the gonads.

GRAHAM, H. B.: *Corpulence in childhood and adolescence: a clinical study*. (*Med. J. Australia*, Nov. 29, 1947, V. II, No. 22, 649-658).

This is a long, exhaustive and possibly important contribution to the title subject written by a physician who is not afraid of giving thyroid extract. Although his regimen contains such important features as dietary and psychological control, the distinctive feature of his work is the fearless administration of huge doses of thyroid extract and thy-

roxine — in fact enough to gain control of adiposity without the danger of undernourishment, which he regards as a worse hazard than producing artificial hyperthyroidism. On the theoretical side, he regards corpulency in childhood and adolescence as of "endogenous" origin, but apparently he means by this that the condition is hereditary and dependent on the whims of the genes. He does not mean that it is possible to strike a definite constitutional or endocrinous formula to cover the condition. The reviewer saw no reference to basal metabolic readings. Thyroid extract is regarded merely as a therapeutic tool which, despite the risk of overstimulation, should be used boldly to accomplish the purpose of weight reduction!

SCHIEER, B. T., CODIE, J. F. AND DEUEL, H. J. JR.: *Weight loss, mortality and recovery in young rats maintained on restricted calories.* (J. Nutrit., V. 33, p. 641, June 1947).

Young rats were kept on low calory diets with the fat content at varying levels. Under diets of very restricted caloric values the loss in weight was less rapid when fat was included. The mortality rate was also smaller when the diets contained fat. On restoration of adequate calories the recovery was better and more prompt when fat was included in the diet. The physical capacity of animals receiving fat was also greater than of animals on isocaloric diets low in fat. The dietary fat probably is essential for certain fundamental metabolic processes and does not exert its beneficial action merely through promoting increased food utilization.

F. E. ST. GEORGE

SUAREZ, R. M., SPIES, T. D. AND SUAREZ, R. M., JR.: *Use of folic acid in treatment of sprue.* (Ann. Int. Med., V. 26, p. 643, May 1947).

Spies and his co-workers report on 22 cases of sprue in the active stages and on 28 cases of sprue kept under control with liver extract. The active or acute cases were treated with a diet poor in meat, poultry, liver, yeast and cheese and an intake of various amounts of folic acid. A daily dose of five mg. folic acid was usually found to be as effective as 50 mg. Small daily doses divided over the day were more effective than a large single dose. An adequate diet increased the effectiveness of folic acid and reduced the requirements for it. Following reduction of the acute stage the remission could be maintained on a daily maintenance dose of 2.5 to 5 mg. folic acid. Of the old cases of sprue maintained on liver therapy a slight to moderate improvement was shown by 19 of the 28 patients when given 10 mg. folic acid every two weeks; the remaining nine patients showed no improvement during a period of six weeks.

B. R. ADOLPH JR.

BELL, E. T.: *The pathological anatomy of diabetes mellitus.* (Illinois Med. Jour., Oct. 1947, V. 92, No. 4, 215-218).

Approximately two-thirds of the deaths in diabetics are due to some complication related to the disease: only 22.3 per cent died of coma and less than one per cent of hypoglycemia. About 80 per cent of the cases of diabetes can now be diagnosed by histological study of the pancreas. A small group can be recognized by a similar study of the kidneys, which show glomerular lesions of two types, of pathognomonic significance when present. Diabetes cannot cause arteriosclerosis but accelerates its development. In most cases of diabetes very few BETA cells are destroyed but they are frequently more or less degranulated. Pituitary growth hormone neutralizes insulin or prevents its formation. The thyroid promotes hyperglycemia by increasing the demand for insulin. The adrenal steroids promote glyconeogenesis.

STEPHENS, C. A., BORDEN, A. L., HOLBROOK, W. P. AND HILL, D. F.: *The use of folic acid in the treatment of aneuia of rheumatoid arthritis — a preliminary report.* (Ann. Int. Med., Sept. 1947, V. 27, No. 3, 420-432).

The use of folic acid improved the blood picture in all of 20 cases of the disease. There was increase in the mean corpuscular volume, the hematocrit, the hemoglobin, the color index and the morphology of the red cells, without comparable rise in the total red cell or white cell counts. Iron did not enhance or detract from the hematinic effectiveness of folic acid. No improvement was noted in the underlying disease, rheumatoid arthritis.

STARR, H. F.: *Insurability of diabetics.* (Southern Med. and Surg., July 1947, V. 100, No. 7, 218-220).

The medical director of the Jefferson Standard Life Insurance Company presents some of the details of the plan by which his company is now able to issue insurance on the lives of selected cases of diabetes mellitus. Naturally, extra premiums are required. The preferred cases are those in whom the disease is not too severe and who are amenable to strict medical supervision. Thus far, the company's experience has been favorable.

WARVEL, J. H.: *The management of diabetes mellitus.* (J. Ind. State Med. Assoc., Sept. 1947, V. 40, No. 9, 854-857).

This paper is a well-reasoned plea for hospitalization and training of every diabetic, since the office treatment does not afford sufficient time on the physi-

cian's part to explain adequately the balancing of diet with insulin dosage.

BLOOMBERG, B. M.: *The effect of p-aminobenzoic acid on experimental typhoid infection in mice.* (S. African J. Med. Sci., Jan. 1947, V. 12, No. 1, 5-15).

Large quantities of PABA were found to inhibit growth on McConkey's medium of the typhoid-paratyphoid group of organisms to a larger extent than that of *B. coli* and other gram-negative, pathogenic, intestinal bacteria. The therapeutic effect of PABA in experimental typhoid in mice was disappointing. Given prior to inoculation it diminishes susceptibility to infection, but PABA has a stimulating effect on the growth of the infecting organism *in vivo*, and in the concentrations which can be used in mice it actually enhances the growth of the bacilli.

BLOOMBERG, B. M.: *The effect of p-aminobenzoic acid on experimental tuberculosis in guinea-pigs.* (S. African J. Med. Sci., Jan. 1947, V. 12, No. 1, 1-3).

Treatment of experimental tuberculosis in guinea pigs with PABA prolongs their period of survival and diminishes the severity of the disease, but does not prevent the development of the infection nor the eventual fatal outcome.

BELL, MURIEL E.: *Protein in the therapy of medical and surgical cases (a review).* (New Zealand Med. Jour., August 1947, V. 46, No. 254, 255-263).

The importance of protein in growth, repair, enzyme formation, movement, secretion, excretion, production of antibodies, hormones, for plasma proteins, in the detoxication of certain poisons, in the formation of hemoglobin and for determining the constitution of chromosomes, is stressed. It has been said that proteins are not only the building material but also the workmen that do the building. Skim milk powder is a good source of valuable amino-acids, including methionine. Causes of protein deficiency include insufficient intake, impaired digestion or absorption, inadequate synthesis of plasma proteins, increased breakdown of body protein, excessive loss as in ascites. Protein feeding may be required in bleeding peptic ulcer, chronic pancreatitis, enteritis, ulcerative colitis and duodeno-colic fistula, etc.; hepatitis, infection, diabetes, thyrotoxicosis, anemia, premature infants, pregnancy and other conditions.

STEWART, C. P.: *The biochemistry of senescence.* (Brit. Med. Jour., Oct. 11, 1947, 569-571).

The author is not so much interested in an "im-

mortality" for man (which obviously is impossible) as in prolonging man's years and adding "life to his years," by increasing the time for his use of his accumulated skills and wisdom. The basal metabolic rate is reduced in later years. There is an increasing tendency to anaecidity and achlorhydria with the passage of the years. Glucose tolerance appears to be lowered in old age. There is a decreased concentration of plasma proteins. In rats it has been shown that a diet qualitatively well balanced but quantitatively insufficient for rapid growth promotes longevity and postpones the changes associated with old age. Perhaps we are wrong in overfeeding our children and producing rapid growth. Excessive fat intake, especially cholesterol, promotes arteriosclerosis. It is quite possible that changes in the permeability of cell membranes cause interference with both anabolism and catabolism, with consequent adverse effects on the aging organism.

BROOKS, C. M.: *Appetite and obesity.* (New Zealand Med. Jour., Aug. 1947, V. 46, No. 254, 243-254).

This is an "exhaustive resume" of the title subject, the main conclusion of which is that obesity is an abnormal condition caused by excess storage of potential energy-producing substance in the form of adipose tissue. Adiposity due to bilateral injury to the hypothalamus is described. Obesity is not a phenomenon of endocrine abnormality. The commonest form of human obesity is due primarily to psychological causes. Over-eating can be used as compensation when other common channels which normally bring satisfaction are blocked. The cause of obesity is merely the ingestion of more food than is required to meet the individual's energy output. The treatment of obesity by starvation and low calorie diets is always successful in reducing weight. The cure of obesity depends upon reacquiring other activities and interests which are capable of dwarfing the importance of eating.

HARRIS, L. J.: *All the vitamins* (Brit. Med. Jour., Nov. 1, 1947, 681-684).

This article was written at the Editor's request to help answer the common question — "give a list of vitamins with all their different names and with notes on the signs and symptoms of deficiency." The vitamins which so far have been shown to be needed by man are the following:— vitamin A, vitamin B₁, three components of the vitamin B₂ complex, namely nicotinic acid, riboflavin and folic acid — vitamins C, D, and K. together with several different forms and modifications of most of them. Of uncertain human value are — two additional "B₂ vitamins" (biotin, vitamin H, and choline), and also vitamins E, F, and P. A third group of vitamins are those demonstrated only by means of animal experimentation. These consist of four vitamins of the B₂ group (vitamin B₆, pyri-

doxine, pantothenic acid, inositol, p-aminobenzoic acid). Vitamin F is a synonym for the nutritionally essential unsaturated fatty acids — linoleic acid, linolenic acid and arachidonic acid.

WHEATLEY, D. P.: *Vitamin K for the relief of chilblains*. (Brit. Med. Jour., Nov. 1, 1947, 689-691).

Synthetic vitamin K (acetomenaphthone) was administered orally to eight persons suffering from chilblains of various grades of severity. In all but one, good results were obtained. The author's reason for carrying out this clinical experiment was based on the observation that defective peripheral circulation with increased permeability of the vessel walls and diminished coagulability of the blood, were features of the perniotic syndrome.

MISCELLANEOUS

SEIBOLD, G. J.: *Allergy of the gastro-intestinal tract*. (Texas State Jour. Med., Oct. 1947, V. 43, No. 6, 377-381).

Allergic manifestations in the digestive tract are manifold and can mimic pylorospasm, cyclic vomiting, peptic ulcer, and cholecystitis. Allergic reactions may result not from foods alone but also from drugs, biological products, antibiotics and bacteria. Food diaries and elimination programs are the chief sources of information in attempting to discover the provoking factor. Pyribenzamine and benadryl furnish the best control of symptoms though adrenalin and morphine may at times be required. Surgery ought not to be too long delayed in acute abdominal disturbances.

CARDON, L.: *A new sign in the diagnosis of minimal and moderate ascites*. (Illinois Med. Jour., Oct. 1947, V. 92, No. 4, 239).

In the presence of a slight to moderate amount of ascites, a fluid wave otherwise unobtainable may be elicited and a slight or questionable fluid wave may be accentuated by examination of the abdomen during the momentary expiratory phase of a cough or while the patient strains against the closed glottis.

ROSE, P. A.: *Treatment of rheumatoid arthritis*. (Illinois Med. J., Sept. 1947, V. 92, No. 3, 175-181).

Ninety-one cases of rheumatoid arthritis were treated with aurothioglycolanilide ("Lauron," Endo Products, Inc.) an insoluble gold compound, containing 54.3 per cent of gold. Complete symptomatic relief was obtained in 44 cases and marked improvement in 22 other cases, making a total of 73 per cent of

satisfactory clinical results. Toxic manifestations were few in number and not serious.

HINDMRASH, F. D.: *Bile peritonitis in infancy*. (Brit. Med. Jour., July 26, 1947, 131).

This is a description of the first reported case in Britain of bile peritonitis in infancy occurring without trauma. Pre-operatively the symptoms and signs suggested a perforated appendix and peritonitis. The peritoneal cavity was found filled with bile, and the patient was cured by simple drainage. No lesion was found. Possibly there may have been a small cyst or aberrant duct which had ruptured.

THOMPSON, R. B.: *Thrombosis of the hepatic veins*. (Arch. Int. Med., V. 80, p. 602, Nov. 1947).

Over a hundred cases of the Budd-Chiari syndrome were collected from the literature to which two are now added. The pathology consists principally of venous thrombosis of the hepatic veins or vena cava, resulting in venous engorgement and necrosis of the liver. The initial obstructions are due to a variety of conditions such as endothelioma, hypernephroma, carcinoma, polycythemia, gumma, leukemia, etc. The youngest patient was one year and 17 months, the oldest 61 years, and the average 34 years. A congenital vascular fault may be a factor in some cases. Vascular injury, as from the repeated coughing in pertussis, has been suggested. Phlebitis of the hepatic veins with cellular infiltration of the media is probably an important factor in many cases. The early clinical features are abdominal pain and indigestion, and later hepatic enlargement, ascites, caput medusae, splenomegaly, jaundice and edema. Vomiting occurs during acute phases in one quarter of the cases. Diarrhea is infrequent. Treatment is that for portal cirrhosis. Operative interference hastens a fatal termination.

STEPHENS, C. A. L. AND OTHERS: *The use of folic acid in the anemia of rheumatoid arthritis*. (Ann. Int. Med., V. 27, p. 420, Sept. 1947).

A series of 20 patients with rheumatoid arthritis were given folic acid. With doses that were effective, there was a dramatic improvement in the blood picture but even sustained treatment had no effect on the diseased joints. The hematocrit, mean corpuscular volume, hemoglobin and color were increased without an actual increase in the red cell count. The leukocytes were unaffected. With the folic acid therapy there was an increase in immature red and white cells in the peripheral blood. Other anti-anemic substances have not been known to produce this phenomenon in rheumatoid arthritis. The addition of iron to the folic acid did not alter the latter's hematologic effectiveness.

LEVY, H.: *Folic acid in pernicious anemia — effects shown by serial sternal punctures.* (Brit. Med. J., No. 4499, p. 412, March 1947).

The subject was a patient with pernicious anemia in relapse. Hematologic and neurologic studies were followed through. A single dose of 50 milligrams of folic acid was given by mouth. Nucleated red cells with basophilic cytoplasm increased rapidly in proportion. The sternal puncture marrow smears showed that the disturbed granulopoiesis was not influenced by the folic acid.

GORDON, I., INGRAHAM, H. S., AND KORNS, R. F.: *Transmission of epidemic gastroenteritis to human volunteers by oral administration of fecal filtrates.* (J. Exp. Med., V. 86, p. 409, Nov. 1947).

During the fall and winter months of 1946-47 there were outbreaks of gastroenteritis of epidemic proportions in several New York state institutions. The symptoms which persisted on the average for three days, were a sudden precipitation of diarrhea and frequently also vomiting but without hyperthermia. There were several fatalities but neither post mortem findings nor bacteriologic studies revealed the causative agent. By administration of suspensions of stool from the affected subjects to human volunteers the agent was shown to be transmissible and filtrable. Inhalation of sprayings from throat washings from affected subjects was ineffective; the gastroenteritis developed only after oral ingestion.

DOAN, C. A., WISEMAN, B. K., AND OTHERS: *Radioactive phosphorus P_{32} . A six year clinical evaluation of internal radiation therapy.* (J. Lab. Clin. Med., V. 32, p. 943, 1947).

In addition to Doctors Doan and Wiseman, the other co-authors of this timely paper are C. S. Wright, J. H. Geyer, W. Myers and J. W. Myers. The results of treatment of 100 cases in the hospitals associated with Ohio State University are reviewed. The radioactive phosphorus was given intravenously as dibasic sodium phosphate or else orally as potassium dihydrogen phosphate. The susceptibility of the individual as well as of different tissues showed great variations.

Long symptomatic remissions were produced in polycythemia vera. The hematologic picture was also improved. However, reduction in platelet and white cell counts preceding reduction in red cell count often necessitated discontinuing treatment with radioactive phosphorus. In chronic lymphatic leukemia the response varied from poor to good; the intractable itch often present was usually abolished even in cases where roentgen ray therapy was ineffective. In chronic myelogenous leukemia radioactive phosphorus did not produce as good results as roentgen ray therapy, but was recommended when roentgen rays were not tolerated. In Hodgkin's disease the use of radioactive phosphorus is dangerous because all types of blood cells may be decreased.

Metastatic bone tumors were apparently not caused to regress but relief from pain for periods of two weeks to six months was brought about by treatment. Leuk-sarcoma remissions were few and of brief duration.

A Critique on Vagotomy, Part I. Historical and Experimental

By

J. A. SCHILLING, M.D.

ALEXANDRA FELDMAHN

and

W. J. MERLE SCOTT, M.D.

ROCHESTER, N. Y.

THE INTEREST IN VAGOTOMY as a surgical method in the therapy of peptic ulceration of the stomach and duodenum, has prompted us to make an extensive review of the literature with special regard to early experimental studies, the first application of this experimental method to man, and to more recent physiological studies. A careful attempt has been made to review every publication that might be pertinent, though undoubtedly significant papers on this subject have been overlooked. During the last two and one-half decades, four excellent, though limited reviews of more recent literature have appeared. (McCrea (80), Hartzell (53), Cameron (19) and Small (117)). An attempt has been made to avoid repetition of these papers and at the same time to correlate the information up to the present era.

Thomas Willis (135) in his *Nervorum Descriptio et Usus* gives what is probably the first accurate description of the origin and distribution of the "Wandering Pair" or the "Par Vagus," which he considered the eighth cranial nerve. Previous to this, Crookes (22) in 1631, because of the extensive distribution of this nerve in the chest and abdomen, referred to the Vagus as the gadding or wandering seventh conjugation, or the seventh cranial nerve Conjugatic vaga. Galen considered the vagus as the sixth cranial nerve. Prior to Willis' description there had also been considerable confusion about the significance of the cervical ganglia, the relation of the vagus to the hypoglossal, the spinal accessory, and the sympathetics. Vesalius (127) had described the sympathetic and therefore the splanchnics as branches of the vagus just as Galen, Hippocrates, and other ancient writers had done before him. In the middle of the nineteenth century the eminent French neurologist, Longet (77) advanced the theory that the spinal accessory and the vagus nerve were analogous to the motor and sensory roots of a spinal nerve and that all the motor functions of the vagus were actually due to fibers of the accessory. This concept was accepted and taught for many years until van Gehuchten (42) and his co-workers proved by their experiments and careful histological studies that it was erroneous. In 1901, in his paper on the connections between the "nerve of Willis" (spinal accessory) and the pneumogastric,

van Gehuchten gives a very interesting table of the conflicting findings of 19 different investigators who studied this problem between the years 1832 and 1898.

The function of the vagus nerve early attracted the attention of investigators. Galen (41) observed that sectioning the recurrent laryngeal nerve caused animals to lose their voice. He also reports the case of a physician who wanted to remove a swelling deep in the neck and being afraid of rupturing a vessel did not use a knife, but separated the membranes with his fingernail. "In his ignorance" he did not notice that he had severed the recurrent laryngeals and was amazed that though the child was cured of his ailment, he became mute. In discussing the organs of nutrition, Galen (40) praises nature for endowing the gastro-intestinal tract with great sensibility. He says "this sensibility does not always prevent lesions, since the acidity of the contents may cause ulceration and erosion of the tunic, or the accumulation of matter cause injury by pressure, but what damage would be caused if the intestines were insensible? It is for this reason that each intestinal fold is provided with a branch of a nerve as well as an artery and vein."

Haller (50) in his studies of the vagus maintained that food was not digested after vagotomy and began to ferment. Early in the nineteenth century there was a great interest in the effect of sectioning the vagus. The prevalent opinion was that vagotomy abolished the power of chymification. Magendie (83) did not conform to this opinion, however, and observed that most of the experimenters were sectioning the nerve high in the neck and believed that the derangement of digestion was chiefly a secondary effect due to the impairment of respiration and pulmonary circulation caused by the operation. To prove his theory, he divided the nerves in the thorax, immediately above the diaphragm by introducing his finger into the chest after dividing one of the sternal ribs, and raising the esophagus. Some time after the division of the vagi, he compelled the animal to eat and found that the substance ingested had undergone chymification.

Paetsch (94) in 1822 in his medical thesis discusses Magendie's theory in the course of his review of previous literature, that included statements of the work of Galen, Petit, Willis, Lower, Haller and Brunn

From The Department of Surgery, The University of Rochester, School of Medicine and Dentistry, Rochester, New York.

on the vagus nerve. In testing the direct or indirect effect of the vagi on digestion he used carefully controlled dogs in pairs. He utilized the abdominal approach for sectioning the vagi and became conscious of their many variations. Hesitating to disagree completely with the theory of Magendie, he cautiously states that the integrity of the vagi was one of the necessary conditions for good digestion. Bichat (12) observed that irritation of the vagus caused contraction of the stomach. In his pursuit of the question of the relationship of nervous impulses to glandular secretion raised by Home (55) in 1806 and earlier by the famous Swedish chemist, Berzelius (10), Brodie (18) in 1814 observed that vagotomized dogs died following arsenical poisoning without the usual copious diarrhea and vomiting of the control non-vagotomized animals. Dr. Wilson Philip (99) around 1818 created further controversy on this subject by his experiments in which he divided the vagus nerves in two animals after they had eaten heartily and stimulated the peripheral ends of the nerves in one animal with a galvanic current. According to Philip, digestion was abolished in the one animal but in the second with galvanic stimulation, digestion proceeded as if the nerves were intact. These results were submitted to a special commission appointed by the Royal Society in which Brodie was a member. Apparently these results were not confirmed. Other investigators, however, reported observations similar to Philip's, while some only stated that sectioning the nerves weakens gastric function. At a much later date, 1870, Wood (140) repeated Brodie's experiments and demonstrated that cathartics and emetics were ineffectual after vagotomy. However, in a second publication (141) after further work, he concluded as had Magendie many years before, that changes were due to an accumulation of carbonic acid through interference with the lungs and circulation. Ware (131) in 1828 published the first account of experimental vagotomy obtainable in this country. He severed the vagus nerves of cats and rabbits in the neck. He reported that digestion was arrested and that there was a deficiency in the action of the muscular coats of the stomach. Secretion seemed to be augmented but ineffectual in digestion. Sedillot (109), in 1829, completely reviewed the literature on this subject, which was quite extensive, even at that period. On the basis of his experiments, performed on various classes and types of animals, he concluded that the effect of the vagus on the digestive functions of these various classes of animals was different. He observed that the contractions of the esophagus and the peristaltic movements of the stomach as well as the secretion of the left portion of this organ, were under the special influence of the vagus. Claude Bernard (9), in very accurate observations, described a cessation of gastric contractions, an arrest in secretion, and abolition of sensitivity of the stomach following section of the vagi. Shortly thereafter, in 1860, Schiff (111) stated that the activity of the stomach was not wholly dependent on the integrity of the vagi. He criticized many previous experiments because of their short and acute

nature. Schiff's concepts regarding the effect of vagotomy on gastric secretion, sensitivity, hunger, thirst and motility are quite similar to our present opinions. He suspected that diseases of the brain often affected the stomach. He stated that Brachet (17) was the first in 1825 to point out that the variable results obtained by different investigators were probably due to incomplete section of the vagi. Brachet maintained that if only the two or three main vagal trunks were severed, other important fibers in the esophageal wall were left often uncut. Ravitsch (105) in 1861 concluded that the vagus nerve was the only motor nerve of the stomach. Adams (1) wrote a very excellent review of the known facts concerning the vagus nerve in 1873. Pavlov's (98) classic experiments begun in the latter decades of the 19th century and published in English in 1910, introduced the modern era of experimental gastro-intestinal physiology. Pavlov established the vagi as the efferent pathway for the cephalic phase of gastric secretion, and noted the classic effects of vagus section. In 1947, Frumin and Kovalevski (39), in Russia repeated Pavlov's original experiments on humans who had esophagectomies and vagotomies because of corrosive strictures of the esophagus. Observations were made on four patients, three of which had esophageal resections and vagotomy and the fourth with a gastric fistula and intact vagus nerves was used as a control. The experiments were carried out one month after operation according to all the rules of Pavlov. Sham feeding in the control produced a copious gastric secretion high in acid and pepsin. In the three vagotomized patients there was a continuous gastric secretion low in acid and pepsin. This continuous secretion was not altered after sham feeding.

Shortly after 1900 the development of positive pressure anesthesia had permitted attempts at resection of esophageal carcinomas. Accordingly, surgeons in Germany (Starck (119), Rubaschoff (106), Frouin (38), Fritsch (37), Unger (125), Litthauer (75)) were interested in the effect of vagotomy at lower levels. Numerous papers at this time stressed the fatal effects of bilateral vagotomy in the neck clinically and experimentally to such an extent that cases surviving unilateral vagal section were reported. (Dechanow (24), Widmer (133)). At this time Heller and Weiss (54) advocated the use of novocain injection into the vagi during their supra or infra-diaphragmatic manipulation for high gastric or low esophageal neoplasms. The experimental work of the above investigators and surgeons revealed the now well-known effects of vagotomy and their reports led others to apply the procedure to various gastric disorders, particularly tabetic crises. (Exner (35), Bircher (13)). The vagotonic syndrome, emphasized by Eppinger and Hess (33, 34) was considered a suitable indication for vagotomy by one of several methods, all of which were below the diaphragm and all were incomplete. Following the first world war this work was continued. Stierlin (121), Steinthal (120), Latarjet (70, 71), Schiassi (110), Pauchet (96), Giannolla (43), and undoubtedly others performed

various types of incomplete or partial vagotomies on human beings. In general the indications for vagotomy were vague, studies were inadequate, follow-up was too short, and diagnoses often were never established. McCrea in 1926 (80) reviewed all the previous clinical and experimental data and concluded, despite adverse opinions by Borchers (16) and Koennecke (67), that there was a definite place for vagotomy in the treatment of peptic ulcers. Little has been added in recent papers to the excellent anatomical studies and descriptions of McCrea and his associates, (52, 78, 79, 81, 82). During this period and shortly thereafter Ranson (104) and his associates carried out extensive investigations regarding the anatomy and histology of the vagus nerve. Lauwers (72) in Belgium arrived at conclusions similar to those of McCrea and emphasized as had many of the early physiologists that completeness of vagotomy was an essential. He pointed out that the Latarjet operation, which had received wide attention, was not a pure vagotomy, but a section of all of the extrinsic nerves of the stomach. Grimson and his associates (46) have recently published a paper concerning the early clinical results of transabdominal celiac and superior mesenteric ganglionectomy, vagotomy, or transthoracic splanchnicectomy in patients with chronic abdominal visceral pain. Thus, the cycles of operative methods have a tendency to repeat themselves. However, these authors state that vagotomy should not be employed for gastric crises and probably should not be used at the time of ganglionectomy for visceral pain. In this regard, Lauwers devised an infra-diaphragmatic approach similar to Dragstedt's. Mayo (86) in 1927 performed incomplete vagotomies for pylorospasm. Pieri (100) in 1927 first described and used a supra-diaphragmatic transthoracic approach to the vagi in the treatment of peptic ulcers. In subsequent papers, (101-103) he reported an infra-diaphragmatic approach with mobilization of the esophagus, and division of the triangular ligament of the liver, practically identical to the method resorted to recently by Dragstedt. Unfortunately, no follow-up reports on his cases have appeared to our knowledge, though apparently good results were achieved with no serious complications over a period of at least five years. Hartzell (53), after a complete review of the literature, approached this problem experimentally in 1929 and used a transthoracic approach in his dogs. VanZandt (126), in 1932, noted a return to normal function and secretory values after a period of one to two years. Bircher (14) in 1931 wrote an excellent treatise on this subject and summarized his clinical experiences that dated back to 1911. He felt that the spectacular results of some drastic operative procedures had made surgeons forget the numerous physiological functions and complicated nervous system of the stomach. He stated that hyperacidity and hypermotility of the stomach could be controlled by operating on the vagus. With an experience related to 150 patients he found good results could be expected in 75%. He employed bilateral vagotomy at the cardia with or without section of the sympathetics at the pylorus. A gastro-

enterostomy or pyloroplasty was used in certain instances. Results tended to improve over a period of ten year follow-up rather than to become worse. However, it may be noted that indications for vagotomy often included the vagotonic syndrome, ptosis and presumably tabetic crises and ulcer, though no clear cut diagnoses were presented. Also vagotomy undoubtedly was incomplete in many cases. In a personal communication, Bircher (15) mentions that he performed his first vagotomy in 1911 and that after 36 years of experience, he considers it a valuable procedure. Twelve patients seen recently "sich seit Jahrzehnten nach der Operation ganz wohl und vollkommen geheilt befinden."

Beaver and Mann (7) in 1931 attempted to protect dogs from jejunal ulceration by vagotomy after the Mann-Williamson procedure (84). The groups of control and experimental animals were unfortunately too small in number to be of statistical significance. Recently Harkins and Hooker (51) have repeated these experiments and found that 11 of 13 control dogs died with ulceration while only one of nine dogs died of ulceration when a transthoracic vagotomy was added as a second stage to the Mann-Williamson procedure. Saltzstein (107) and his co-workers on the other hand failed to protect their Mann-Williamson dogs by vagotomy. A marked jejunitis distal to the anastomosis was a prominent feature of the pathological findings. Oliver (92) also failed to protect Mann-Williamson dogs with vagotomy.

Cushing (23) in his famous Balfour lecture demonstrated conclusively the importance of the central nervous system in certain cases where peptic ulcers developed in the course of intracranial lesions in the hypothalamus. This work has been substantiated clinically by Ask-Upmark (4). The vagus has been shown experimentally to be the pathway for the noxious stimuli in intracranial lesions by Keller (63, 64). Singer (116) in 1916 first suspected organic lesions of the vagus nerve itself as the cause of certain cases of pyloroplasm and gastric hemorrhage without demonstrable ulcer. In one case reported, a tuberculous lesion was found involving the right vagus. Stahnke (118) in 1922 was able to experimentally produce gastric erosions and ulcerations by repeated stimulus of the vagus nerve. This could not be confirmed by Best and Orator (11) ten years later. Manning, Hall and Banting (85), however, reported congestion and hemorrhage of the mucosa of the duodenum and pylorus following vagal stimulation that could be abolished by atropine and accentuated to the extent of ulcer formation by eserine administration. Husten (56) in 1924 was of the opinion that the motor nucleus of the stomach and esophagus was in the spinal portion of the dorsal nucleus. These conclusions were reached after sectioning the vagi peripherally at various levels and noting the area of central degeneration.

The psychosomatic aspect of peptic ulceration is of importance here. Experimentally, the vagus nerve has been shown to be the pathway for the cephalic

phase of digestion and also for noxious stimuli produced intracranially experimentally. Presumably then, the vagus nerve is the pathway for stimuli of psychic origin. Alexander (2) emphasized in 1934 a marked dependency and intense receptive and acquisitive wishes in ulcer patients. These tendencies are repressed and produce violent conflicts that manifest themselves in the ulcer syndrome. Von Bergmann (8) was one of the earlier authors to stress this. The direct observations of Wolf and Wolff (139) corroborate these conclusions. Erythema and even ulceration of the gastric mucosa could be precipitated by mental conflicts produced in their diener Tom. Recently, Kapp, Rosenbaum, and Romano (62) have described ulcer patients who have developed different defense mechanisms to the conflict over intense dependent desires. These patients fall into three main groups. The first is the accepted ulcer type, namely the hard driving, outwardly independent, successful individual, where this overt behavior represents an over-compensation for deeply repressed, intense receptive desires. The second group is the fairly successful, outwardly meek, shy and effeminate personality where the dependent longings are partially conscious. The third group reveal a severe character disorder, a psychopathic personality, inability to earn a living, alcoholism, gambling and delinquency. Here the dependent desires are expressed in irresponsible, child-like overt activity and demanding impulses. (In our experience a group three type personality is a contra-indication to vagotomy).

During the third and fourth decades of this century, Klein (65), Winkelstein (136-138), Shapiro (113-114), and Weinstein (132) in a series of papers from the Mt. Sinai Hospital in New York City reported the use of vagotomy in addition to definitive procedures on the stomach for the treatment of peptic ulcer with questionable results. Unfortunately their careful studies were obviated by incomplete section of the vagi and lead to adverse opinions concerning the value of the procedure. Barron (6) used a right vagotomy unsuccessfully in a patient with peptic ulcer. Ferguson (36) experimentally divided the vagi intrathoracically in monkeys with results that led him to question the value of vagotomy in peptic ulcer. He noted many mucosal erosions in the stomachs of his animals. This may be quite important in light of the gastroscopic observations of Paulson and Gladson (97) and Grimson (44) recently in vagotomized patients. These investigators noted that there was marked edema, thickening and nodular-like hypertrophy with or without erythema and friability of the remaining gastric mucosa after subtotal gastric resection and vagotomy. Without a gastro-enterostomy there was little mucosal change and the pylorus and antrum were patulous. Wilhelmj (134) and his associates employed transthoracic vagotomy in dogs followed later by partial gastrectomy with no evidence of return to normal acid levels after three months observation. They stated that the intestinal phase of acid secretion was very marked and unusually prolonged. Edwards (32) in 1938 concluded after care-

ful anatomic dissections that the vagi could be completely dissected below the diaphragm and that this procedure should be useful in the treatment of peptic ulcer.

The relation of the vagus nerve to mucus and pepsin secretion, though unknown to its basic aspects, has received considerable attention. Mucus is considered a protective agent by Wolf and Wolff (139) and also by Ivy (59). Jennings and Florey (60) believe that the vagus controls the secretion of mucus in the cardiac, pyloric and fundal areas. Vineberg (128) observed on weak stimulation of the vagus nerve, a flow of viscid mucus from the stomach. On strong vagal stimulation a flow of gastric juice occurred with a very high digestive power, high acidity, but small amount of mucus that was thin in character. Many recent papers stress the thick viscous mucoid character of gastric secretion after vagotomy. Loeper and Fau (76) have reported an enlargement of the mucous cavities of the cells in the fundus and an increased layer of mucus covering these cells after vagotomy. A thick viscid mucus may be independent of vagal stimuli, though seems to increase after nervous activity (Babkin (5). Local mechanical irritation was found to stimulate mucous secretion. Savitch (108) noted a high mucus content in response to sham feeding in dogs. Ihre (58) feels that mucus binds, neutralizes, and dilutes gastric acid, possessing also a buffer activity and absorbing pepsin. In considering the relation of the vagus nerve to mucus secretion, its importance has probably been underemphasized and it is regrettable that more precise knowledge is lacking concerning its composition, conditions of secretion, and role in digestion and prevention of ulcer formation.

Though the mechanism of secretion of pepsin is still obscure, it is now being assigned a more important role in the causation of peptic ulcer. Ihre (58) has definitely shown that pepsin secretion is under vagal control. Using insulin as the stimulus, he noted marked increases in pepsin content of gastric secretion. By direct vagal stimulation, a pepsin power of gastric juice is produced that exceeds that obtainable by sham feeding. According to Babkin (5), histamine does not stimulate pepsin, though increased hydrochloric acid secretion causes a washing out of pepsin into the gastric content. Pepsin secretion is not abolished by vagotomy (Moore (88). Frumin and Kovalevski (39), referred to earlier, noted reduced pepsin content of the secretions of the gastric pouches of humans after vagotomy with no increase after sham feeding. Recently, in an excellent presentation, Le Veen and Hollinger (73, 74) demonstrate that pepsin activity may be predicted by the law of mass action and it is directly proportional to the concentration of pepsin and active substrate. Pepsin is inhibited by the peptones and their quantity determines the amount of active pepsin. A low pH seems to be the most important factor in high peptic activity. The pH of gastric secretion of ulcer patients is significantly lower and the resting peptic activity is higher than normal

subjects. This helps to more adequately explain the earlier results of Schiffrin (112) and Koulouck (68) who found in perfusion experiments that true ulcers can only be formed by acid-pepsin mixtures and not by acid alone. It may also help to explain the beneficial effects of vagotomy where pepsin secretion is reduced, where the pH of the gastric juice is higher, and where accordingly the peptic power is markedly reduced.

The question of esophageal dilatation and paresis following vagotomy and the question of regeneration of the vagi are of clinical interest. A few experiments have been recorded regarding these problems. Claude Bernard (9) first described esophageal dilatation and paralysis in the rabbit after vagus section in the neck. Edwards (32) produced megaesophagus experimentally by dividing the vagi high in the thorax. Knight (66) observed that complete bilateral vagus section in cats produced achalasia which could be modified by sympathectomy. Rubaschoff (106) in 1912 concluded that section of the vagi in dogs above the level of the pulmonary hilus resulted in paralysis of the lower end of the esophagus. These conclusions have recently been re-established by Hwang, Essex, and Mann (57) who felt that peristalsis of the lower two-thirds of the esophagus was dependent on the extrinsic vagal nerve supply. Shay and Komarov (115) have also noted esophageal dilatation in rats. Ozorio (93) also noted chronic dilatation of the esophagus in dogs after section of both vagi in experiments designed to mimic the disease "mal de engasgo," noted in certain rural sections in Brazil, and thought by some to be due to chronic vagal lesions. This disease is characterized by dilatation of the esophagus. Thus on the basis of animal experiments one may expect certain cases of esophageal paresis clinically. This may be particularly true when the surgeon's zeal to do the necessary complete vagotomy, leads him too high in the thorax.

Regeneration of the vagus and potential recovery of function by cross communications with the sympathetics in the thorax and abdomen are particularly important questions in considering the long term effects of vagotomy. Experiments on the regeneration of the nerves were begun as early as 1795 when Haighton (49) sectioned the vagus in one side of the neck in dogs, and then at later periods up to six weeks, sectioned the opposite vagus. The last animal survived this experiment, but was mute. Nineteen months later both vagi were simultaneously sectioned a second time at a lower level in the neck and this animal promptly died as had original controls. Pathological examination revealed neuromas at the original site of section. From this Haighton concluded that physiological regeneration occurred despite statements by microscopists at that time that the "medium of union did not possess the characters of nerve." Cameron (20) has more recently reviewed this subject in 1933. Using rabbits, cats, dogs, she concluded that regeneration occurs in 3 to 7 months after crushing the vagus and in 1 to 2 $\frac{2}{3}$ years after cutting the nerve.

Stimulation of the nerve distal to the neuroma caused more marked cardiovascular effects than stimulation above the neuroma. Recovery of function of the vocal cords occurred after regeneration, which was confirmed histologically. From this it may be assumed that regeneration may occur when the nerve ends are approximated. However, when whole segments are resected, can the vagus be functionally stimulated by cross communications with the sympathetics in the thorax and abdomen? Duncan (31) completely reviewed this subject in 1928 and utilizing cats, dogs, and rabbits concluded that there were gross anatomical connections between the vagus and the thoracic sympathetics. There was practically no evidence of myelinated vagus fibers entering the sympathetic nervous system through the thoracic sympathetic trunks. However, three exceptions to this statement made it impossible to conclude that there were absolutely no connections. McSwinnery and Spurrell (81) concluded that the functional path of the vagus is confined to that nerve and has no essential connection with the sympathetics. In addition to visceral efferents, the vagus contains afferents which were conclusively demonstrated by Partridge and Wilson (95). In current experiments here, concerning the phenomena of drinking behavior in dogs, Towbin (124) is of the opinion that the vagus contains certain afferent nerve fibers. In animals with esophageal fistula, dilatation of the stomach by balloon inhibits drinking only as long as the vagi are intact.

Thus, in summary of the vast clinical and experimental literature regarding the effects of section of the vagus nerve on gastric physiology, there have been several eras of investigation, many different classes of animals have been used, different levels and methods of section and study have been used, and several different groups of investigators have approached these problems.

One may describe the following eras of investigation: 1.) the ancients, Hippocrates, Galen, Vesalius with initial isolated observations. 2.) the 17th and 18th centuries when the general anatomy and extensive wandering distribution of the vagus was fully appreciated. 3.) The 19th century with predominantly physiological experimentation, culminating in Pavlov's classic researches. 4.) The 20th century where clinical application was begun from earlier physiological concepts, where improved methods have allowed bolder surgical procedures and more fundamental research. The psychosomatic concept of ulcer is more firmly established.

Many different animals have been used and these may be classed under four groups: 1.) Omnivorous. carnivorous — man, monkeys, dogs, cats, rats and pigs; 2.) Herbivorous — cattle, horses, sheep, guinea pigs and rabbits; 3.) Cold blooded — turtles, fish, and frogs; 4.) Avians — pigeons and chickens. In all groups, paralysis of the gastric musculature results from vagotomy but is most pronounced in the herbivorous and avian groups where actual obstruction and starvation may occur with a full dilated stomach

or crop. Ulceration of the stomach frequently occurs in rabbits which were the favorite animals of the Italian investigators. The "Ulceri Rotondo" of the rabbit had been early publicized (Zironi (142), Antonini (3)). This led to much unfortunate confusion regarding the effects of vagotomy, an example of which is Lanin's (69) listing of vagotomy as a method of experimental ulcer formation. Another source of confusion in the experimental literature is that of diet of the experimental animal after vagotomy with particular regard to its fluid content. Because of this uncontrolled constant it is impossible to compare many results particularly regarding motility and emptying times. This has been particularly stressed by Meek and Herrin (87). The functions of the vagus as the motor and secretory nerve of the stomach have not been completely discussed. Much of the earlier conflicting data reviewed in numerous publications has become somewhat obsolete when considered in light of the excellent, recent, physiological studies on man following vagotomy. Dragstedt (25-30), Moore (88-91), Grimson (44-48), Harkins (51), Walters (129-

130), and their associates (21, 61, 97, 122, 123). These will be reviewed in detail in part two.

Experimental results have varied because of the type of vagotomy, its level, the completeness, and the secondary complications. High in the neck complete section is easy but mortality extreme because of the obvious complications of recurrent laryngeal nerve paralysis and cardiac tamponade. This level has been used by many investigators, resulting in short acute experiments where the effects of vagotomy have been confused with changes accompanying shock and impending death. Below the level of the pulmonary hilus no lethal effects have been observed, but the results are confused by the question of completeness of section. This is particularly true below the diaphragm. It is now conceded that unless vagotomy is complete, its effects on the gastro-intestinal tract are either absent or variable.

Finally, many types of investigators have approached these problems. Anatomists, pathologists, neurologists, physiologists, veterinarians, internists, and surgeons may be recorded in publications on this subject.

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The Dynamics of Muscle Tonus and Its Relationship to Circulatory Failure

Part III

"A new approach to the treatment of hypertension and circulatory failure by use of the iron salt of the adenylic nucleotide"

By

SIMON L. RUSKIN, M.D.

NEW YORK, N. Y.

KROGH IN A SUMMARY of Yandell Henderson's classical work pointed out that, for many years the circulation was regarded as if the heart action and the vaso-motor (arterio-motor) mechanism were the only variable factors, and as if any failure or depression not due to the former must be due to the latter. Observations by Yandell Henderson (1908) upon an experimental form of shock first demonstrated clearly the occurrence of what he termed "failure of the veno pressor mechanism." This was characterized by decreased and finally inadequate venous return to the right heart, resulting in a decrease in cardiac filling and discharge, while the arteries at the same time were found to be not relaxed, but constricted. Other papers by Henderson and his collaborators, (1909, 1910) brought forward evidence in favor of the view that it is this mode of circulatory failure rather than vasomotor failure which is characteristic of shock, and although there are a number of matters still needing further elucidation, this concept has now come to be generally accepted.

The point that muscle tonus was the key figure in the major mode of death was apparent to Krogh, Henderson and others, yet surprisingly little was done to find a clinical solution for the mechanism of muscle tonus. Sherrington in 1904 had already demonstrated that the greater part of the skeletal

musculature is all the time steadily active. Yet, it seems to have taken a long time to translate the dynamics of the myofibril into terms of muscle tonus and the clinical applications of this dynamics to the control of a "major mode of death."

In two previous papers, the "Role of the Coenzymes of the B complex in Muscle Metabolism" and "The Use of the Adenylic Nucleotide in Muscle Metabolism," the biochemical factors controlling muscle metabolism were presented. This paper is the third of the same series showing the clinical application of the control of muscle tonus.

The dynamics of the circulation may be viewed as a four cylinder mechanism composed of 1.) the heart, 2.) the arteries (vasomotor mechanism), 3.) the veins (venopressor mechanism), 4.) the muscles (myofibril mechanism). Failure of any one of the four power sources can lead to circulatory disaster. While a multitude of enzymatic and direct chemical reactions govern the operations of the four systems similar to the gadgets of a motor car, the actual fuel for the motor is the adenylic nucleotide shifting from adenosine triphosphoric through adenosine diphosphoric to adenylic and back again.

The actual contraction of a muscle fiber and its subsequent relaxation preparatory for the next con-

traction is a function of the shift from adenosine triphosphoric (A. T. P.) to adenylic acid and back again. The energy acquired from the stepwise metabolism of food products in the last analysis goes to supply the energy build up from adenylic to adenosine triphosphate. This energy is used to secure relaxation and is spent during contraction. This is an important and basic conception. When a muscle fibril contracts it may be compared to a collapsing staircase. The build up of the staircase, the stage of relaxation, requires energy, that is the shift from adenosine triphosphate to adenylic acid. In the previous paper I have suggested that the spiral form of micellar arrangement of the protein-adenylic complex comprising the myofibril returns to the spiral form as a result of the spiral pathway of ionic flow from the discharge of the nerve impulse. Thus the nerve impulse not only precipitates the collapse of the spiral form on contraction but also restores it in relaxation.

While the spiral structure of the colloidal micellae is still a matter of question the physical behaviour would seem to support the hypothesis.

Varga has also shown that it is the stage of relaxation of the myofibril that requires the supplying of energy which I have in a previous paper compared to a rubber band that needs energy for stretching and spends the energy in contraction when released. It will be seen later that the persistence of muscle spasm and the contracted state of the blood vessels may be linked to a failure in supply of the energy necessary for relaxation. Hypertension and circulatory failure are linked to this condition.

Varga's experiment quoted by Szent Gyorgi, led to the conclusion "that since the free energy decreases in contraction, we can postulate that this process, being a transition from an energy rich relaxed state to a stabler state, poorer in free energy, occurs spontaneously. Relaxation however can occur only if the free energy of the system is increased by 7,000 calories. The splitting of A. T. P. which according to our present knowledge, is the source of muscular energy, is thus needed for relaxation. The free energy of A. T. P. is unknown; the breaking of one phosphate link liberates 11,000 calories." "A. T. P. thus has two functions. One is a static function independent of splitting. A. T. P. acts as a building stone of the contractile system. Without A. T. P. the actomysin of the myofibril does not contract or relax; it is not reactive at all. The other function of A. T. P. is to provide energy for relaxation."

It is particularly interesting to follow the work of A. Szent-Gyorgi, Straub, Guba, Engelhardt and others in the demonstration of the mechanism underlying muscle contraction in the test tube.

Earlier investigators had shown that a substantial part of the myofibril could be dissolved by strong salt solutions. On dilution a globulin like protein was obtained which they called myosin as differentiated from water soluble myogen. Szent-Gyorgi showed that this earlier myosin was a mixture of two pro-

teins which united to form a compound. Examination showed that the properties of the pure components were quite different from those of myosin itself. Whereas myosin was water insoluble each of the two components were quite water soluble. One of these was named myosin by Szent-Gyorgi to retain the name of the pioneer investigators while the other component discovered by Straub was named actin. While neither of these two proteins is in itself contractile, if put together in proper relation they unite to form actomysin which can be made to contract in the test tube by the addition of adenosine triphosphate (muscle adenylic nucleotide, A. T. P.) and ion constituents of the muscle fibre. It was a dramatic experience to see Szent-Gyorgi's demonstration of this synthetic "muscle" contraction.

It is not chance that the adenylic nucleotide is the fuel for muscular contraction and relaxation. Rather, nature has built the entire hemodynamics around it. Not only does the heart muscle contract by virtue of the adenylic-adenosine triphosphate set up, but the coronary artery dilates to increase the heart blood supply. If the heart muscle power were increased when the peripheral vessels were narrowed and not prepared for the additional heart power it would be faulty dynamics. This nature has also provided for by the peripheral vasodilatation produced by adenylic acid. Likewise, the increased muscle fibril contractility supplies the venopressor mechanism. Thus all four factors in hemodynamics are simultaneously served by the adenylic nucleotide.

As a still further aid to the energy mechanism, the adenylic nucleotide itself participates in the enzymatic breakdown of carbohydrate by phosphorylating the elements of the B complex thus converting thiamin to the coenzyme cocarboxylase, riboflavin to riboflavin phosphoric acid and nicotinamide to coenzyme I and II. In this manner it aids in the release of energy from nutrition by the stepwise utilization of the hydrogen atom in the carbohydrates. However, the end step of this nutritional utilization involves the final oxidation by cytochrome C, a colored iron complex within the cell that is able to take on the oxygen brought to it by another iron compound hemoglobin. To these two compounds may be added the iron salt of the adenylic nucleotide (Ironyl) used in this investigation. So far reaching is the role of the adenylic nucleotide in hemodynamics and muscle metabolism that the adenylic nucleotide as shown by Ruskin and Katz is itself a potent stimulus to blood formation causing an elevation not only of the level of hemoglobin but also of red and white cell count. It actually elevates the whole blood picture, provides for an increase in blood supply, participates in the release of energy and itself is a member of the myofibril chemistry in contraction and relaxation.

There is still another side to the role of the adenylic nucleotide in relation to its position as one of the four nucleotides forming nucleic acid which is the basis of gene formation in heredity and the underlying structure of viruses. These aspects will be dealt

with in considerable detail in a subsequent paper based on investigations now in progress.

It will merely be pointed out at this time that viruses are almost pure nucleic acid and the nucleic acid structure is made up of four nucleotides among which the adenylic nucleotide is again the dominant factor. It seems from preliminary studies the poliomyelitis virus may possess the capacity to compete with the myofibril for the adenylic nucleotide and by depriving it of the A. T. P. — A. D. P. — A. M. P. cycle remove the energy for relaxation of the myofibril, thus leaving the muscle in the energy poor spastic state.

It is very interesting to observe that in the correction of the spastic state in poliomyelitis Sister Kenny stretches each muscle and its integuments back to the relaxed state. She thus substitutes a physical elongation as the biochemical equivalent for the A. T. P. relaxation. Her success in this procedure is dramatic to observe. The application of heat also reduces the amount of A. T. P. needed for relaxation since heat increases the effectiveness of A. T. P. and lowers the total requirements.

Szent-Gyorgi points out in an analogy of the myofibril to an actomysin thread that "if contraction and relaxation are two distinct states and the single micels are either fully relaxed or maximally contracted, we can draw conclusions about the equilibrium from the length of the thread. Maximal contractions in this case means that 100% of the micels are contracted whereas no contraction means 0% of the micels are contracted. If the thread shortens maximally from 100 to 30, then this 70% contraction actually means that 100% of the micels are contracted. Contraction half way from 100 to 65 would mean that 50% of the micels contracted producing the equilibrium 1/1. Thus the length of the thread could give direct information about the equilibrium constant at any temperature."

L. Varga considered the muscle fibre to be a similar perfect actomysin thread and used as experimental material the psoas of the rabbit to prove the correctness of the assumption. He also showed that the activity of A. T. P. bore a direct relationship to temperature. Thus at 0° there is no activity. With rising temperature the capacity for muscular activity becomes rapidly stronger to reach a maximum of 68 to 70% at about 16°C. This explains why at 0°C. muscle fibril does not contract. The application of heat thus is A. T. P. sparing.

All of these findings are interesting for skeletal muscle, however, the myofibril of the vascular tree cannot be approached directly either by physical stretching and restoration to the relaxed state or through the application of heat. It can, nevertheless, be reached by the use of the adenylic nucleotide by parenteral injection intramuscularly as has been done for the cases here reported.

With this background of hemodynamics we may now turn to the relationship of muscle tonus to the

vascular tree, which Henderson has pointed out, is a "major mode of death." It is an aphorism that "the first business of the physician is to keep the patient alive long enough for him to get well and in the presence of a severe illness the physician's first step must then be to estimate the patient's vitality, whether it will decrease and he will die." If muscle tonus is the underlying factor in vitality and the survival of the patient, it is well for us to study every factor pertaining to the enhancement of muscle tonus as well as the re-evaluation of commonly used drugs such as phenobarbital and morphine which by reducing muscle tonus may actually hasten the demise of the patient with already low vitality. Likewise the control of excessive muscle contraction in muscular spastic states must be evaluated in terms of additional energy requirements. Thus while a muscle in spasm would seem to be receiving energy for its maintenance, it really is failing to relax for lack of adequate supply of energy since it is the stage of relaxation that requires additional energy rather than contraction.

The use of morphine and phenobarbital for the relief of cardiac pain in coronary occlusion may not be too logical since the pain is the result of ischaemia in heart muscle working under conditions of inadequate oxygenation, anoxemia. Both morphine and phenobarbital decrease the capacity for oxygenation. Thus in Henderson's animal investigations on blood loss and anoxemia the amount of blood withdrawn over a certain time was adjusted so that, if the animals were thereafter left to themselves, approximately half of them died and half survived and recovered. But, if during the hour following the completion of the hemorrhage, even a moderate dose of morphine was administered, all the animals so treated died. The barbiturates are likewise respiratory depressants. What is necessary is increased blood supply, increased muscle tone, increased coronary size. These are a better mechanism for the relief of pain. The adenylic nucleotide, particularly as the iron salt, is probably the most effective agent for this purpose that we now have and provides a new rationale of cardiac therapy. The relief of pain is also more readily accomplished by the direct treatment of the sympathetic at the nasal ganglion.

The correctness of this conception was dramatically demonstrated in two cases of coronary occlusion. One was that of Mrs. Sarah F. who had suffered a typical attack of coronary occlusion accompanied by pain in the left arm and shoulder. After rest in bed for three months she recovered from her precordial pain but continued to suffer pain on motion of the left arm. She came to my office for the relief of shoulder and arm pain. Treatment of the sympathetic at the nasal ganglion was followed by almost immediate relief. In addition she received daily injections of the ferrous adenylate. Her improvement was so rapid that within three days she was following her customary social activities. She received for one week, daily injections of iron adenylate. The patient was not seen thereafter for several months during which time as president of

a philanthropic organization she ran a large theatre party in addition to her other activities. She had been a chronic hypertensive and soon her systolic blood pressure was again over 200 and her diastolic 130. She was now put on barbiturates by her family physician.

One day the patient, while shopping in the neighborhood of my office suddenly suffered sharp, excruciating precordial pain which she described as similar in character and severity to her previous coronary attack. Treatment of the sympathetic through anaesthetization of the sphenopalatine ganglion afforded immediate relief of pain. This was supplemented by an injection of iron adenyate. The energy response and improvement in muscle tone was apparent in a few minutes. The patient was able to continue with her normal work and returned again each day for one week for her iron adenyate injections. Thereafter she received injections twice weekly for several weeks and stated that she was enjoying better than customary health. The speed of her recovery was dramatic.

The second case, Mrs. Lillian O. also suffered a coronary occlusion with the typical severe precordial pains that were not relieved by morphine and phenobarbital medication. She was seen in the evening of the second day of the attack in unabated pain. Treatment of the sympathetic at the nasal ganglion was followed by the first relief since the onset of the pain and the patient rested comfortably for about three hours. In this case however, the attending cardiologist would not change from the routine morphine and barbiturates nor would he use the iron adenyate since he was not acquainted with it or the chemistry of adenylic acid. The patient became progressively worse and died of "cardiac failure." During the treatment of this case the patient received oxygen inhalations. Apparently anoxemia was recognized but they had not realized the fact that circulatory failure was responsible for the tissue oxygen starvation rather than any lack of oxygen in the blood stream. This frequently is not clearly understood. The situation called for improved dynamics of circulation.

It should also be pointed out that the pain in coronary spasm is due to the ischaemia of the heart muscle, not the pain from the spastic artery itself. Lewis has clearly demonstrated this point. As soon as blood flow to the ischaemic muscle is restored, the pain disappears. Morphine and phenobarbital are thus poor seconds to circulatory restoration.

How important prompt restoration of circulation is can be learned from the muscle of the limbs. Lewis has shown that after 15 to 30 minutes from the onset of ischaemia, the nerves to the muscles are paralyzed. When the period of ischaemia is short, 1/2 to 1 hour, recovery of sensory and motor functions is rapid and is complete. When the period of ischaemia is prolonged for hours, the nutrition of the tissues may be affected permanently. The nerves of the limbs lose their function under ischaemic conditions long before muscle becomes inexcitable but long continued

ischaemia kills muscle more readily than it kills nerve. Basing the analogy with the heart it is imperative that blood supply be restored at the earliest possible moment. Blocking the sympathetic gives the quickest aid, while the iron adenyate renders energy support and increased coronary flow. If the coronary attack can be so treated within the first hour of the onset, permanent damage might be avoided. Rest and diminution of cardiac effort also reduces the oxygen needs of the heart muscle and indirectly reduces ischaemia. Oxygen inhalation is unfortunately a far cry from the tissue oxygenation which is required. This can best be accomplished by increased muscle tonus of both the myocardium and the systemic musculature. Measures directed towards improving anemia, supplying the coenzymes of the B complex and amino acid diet are all collateral aids.

Henderson cites two experiments, one of which was conducted with S. C. Harvey in 1908 that is well worth repeating. "The abdomen of a healthy, vigorous dog was opened widely under ether anaesthesia; and the viscera were handled for two hours in a current of air warmed and moistened with steam. Shock was by that time well developed; and the circulation was approaching failure. Analysis of the arterial and venous bloods — the latter from the right heart — at the beginning and near the end of the experiment showed their contents of oxygen and carbon dioxide in volumes per cent to be as follows:

	arterial		venous	
	O ₂	CO ₂	O ₂	CO ₂
At the beginning	15.9	37.4	15.2	39.4
Near the end	15.8	16.1	00.0	33.1

Thus showing complete venous anoxemia, i. e. "oxygen starvation of the tissues" rather than of the arterial blood. Oxygen inhalation would thus add nothing.

The second experiment was performed by Henderson and Barringer using a different method. The thorax, not the abdomen, was opened; the heart was enclosed in a cardiometer and its volume curve was recorded graphically while the pressure in the great veins near the heart was measured. The experiments were not intended to produce shock; quite the contrary. Yet, most of the animals, (vigorous dogs) sank sooner or later into that condition essentially as in the experiments in which the abdomen was opened and the blood analyzed. The succession of events was as follows:

(1) A progressive lessening of the venous return and pressure, and a consequent decrease in the rapidity and volume of the diastolic fillings and systolic discharges of the heart with a more and more thready arterial pulse, but as yet no lowering of arterial pressure.

(2) When the venous return and pressure had fallen to such an extent that the strokes of the heart were reduced to a third or less of their initial volume,

and the output per minute was correspondingly diminished, arterial pressure fell rapidly.

(3) If, at this point, a liberal amount of saline was administered intravenously, the strokes of the heart returned immediately to full normal amplitude and arterial pressure rose again to the normal level; showing that neither the heart nor the vaso-motor system had failed.

(4) Soon, however, the saline leaked into the tissues and the succession of decreasing venous return, decreasing stroke volumes and falling arterial pressure recurred. Another infusion again restored both venous flow and arterial pressure; and this could be repeated again and again, until the total volume of fluid that escaped from the capillaries was so large that the tissues, especially the muscles, were waterlogged.

These two experiments performed by Yandell Henderson many years ago demonstrated that a failing circulation leads to a state of venous anoxemia, oxygen starvation of the tissues, leakage of fluid into the tissues and decreasing blood volume. That an intimate relationship exists between anoxemia, pH and the action of hyaluronidase may soon be revealed thus adding another link to the chain of circumstances surrounding circulatory failure.

The understanding of these factors will play a dominant role in the control of a major mode of death and muscle tonus disturbances.

Physiologists have considered tonus as an interplay between the muscular tissue and the motor centers in the central nervous system. Thus tonus, although evident in the muscles has its seat and control in the gray matter of the spinal cord and hulk and is exerted upon the muscles or reflected through the afferent and efferent nerve fibers back and forth between centers and muscles. Paralysis of the motor pathways brings with it loss of muscle tone. Spinal block too effectively performed extending not only to the sensory roots but also to the motor leads to shock and death.

One is not commonly impressed with the fact that the body at rest is continuously in motion and that that motion is tonus. Actually it is a peculiar form of muscular elasticity. It is by the steadily maintained elastic pulls of tonic muscles that the body is enabled to stand erect and support the head for prolonged periods with a minimum of fatigue. That this characteristic muscular elasticity is a product not only of the muscles but also of the skin and fascia is an observation contributed by that astute observer, Sister Kenny, in her study of infantile paralysis and one which I consider worthy of serious study by physiologists. It is the loss of this elasticity and associated muscle tonus that is responsible for the crippling deformities in infantile paralysis. The earlier this elasticity can be restored and the sooner the muscle tonus can be increased, the less will be the deformity. It was on this basis last summer that preliminary studies

were started for the treatment of the sympathetic at the nasal ganglion supplemented by iron adenylate therapy. It is the maintenance of this continuously acting body tonus in periods of bodily rest that consumes most of the basal energy expenditure of the body, together with its associated heat production, oxygen consumption and carbon dioxide production.

Henderson describes the far reaching effect of body tonus. Without tonus the trunk, the limbs and the face, as seen in facial paralysis, are as limp and sagging as a wet cloth. The chest loses the greater part of its volume, as the diaphragm bellies into the thoracic cavity; allowing the lungs to collapse to an air capacity less than that in the deepest voluntary expiration, and rendering breathing impossible. Such is the condition of the baby that at birth fails to develop sufficient tonus to inflate its lungs — at least partially — and therefore can never breathe. Such also may we consider the condition in poliomyelitis when the diaphragm is affected.

Without the tonic activity of the skeletal musculature the circulation of the blood also ceases so that even if the heart continues for a time to contract and relax, the blood stagnates in the atonic tissues and the heart can pump into the arterial system only such a volume of blood as the venous return brings to it. This is true not only in the new born where neither respiration or circulation can be established without the support of the tonus of the musculature of the infant's body nor can it be maintained in the adult without it.

Tonus thus becomes the indicator of vitality and every factor that adversely influences tonus can induce a train of circumstances leading to circulatory impairment and loss of normal muscle function. Thus as Henderson points out nothing so immediately decreases the signs of tonus as does the inhibiting influence of pain. A painfully wounded man cannot stand. The evaluation of health and disease in terms of general muscle tonus was part of the shrewd observation of the clinicians of the older school and for which laboratory procedures may now be used for recording.

General muscle tonus must not be confused with vaso-motor control of the blood vessels from the medulla oblongata. The muscle tonus of the body is not the arterial pressure but the tonic influence of the motor centers in the spinal cord upon the skeletal musculature. The importance of this point cannot be overstressed. It is particularly significant when caudal or spinal anaesthesia is being used. The elimination of the impulses from the spinal cord may be followed by failure of muscle tone not only of the voluntary muscles but also of the involuntary, particularly the uterus during childbirth. Loss of tonus could lead to failure of post partum contraction and fatal uterine hemorrhage. The elimination of spinal impulses in spinal anaesthesia may lead to failure of venous return through loss of muscle tone with ensuing circulatory collapse.

The addition of blood by transfusion is a temporary effective aid but is no answer to the problem since the "booster pump" of the muscle fibril is no more capable after transfusion than before. The restoration of circulation calls for the rhythmic contraction of the muscle fibril and efforts must be made in that direction by restoring the nerve impulses from the spinal cord by: (1) increasing the sensitivity of the spinal cord to all impulses, (2) increasing the motor end plate sensitivity, and (3) increasing the energy supply and contractile efficiency of the muscle fibril.

Tonus and venous return may be considered as inseparable and the remarkable arrangement of the intramuscular blood vessels to accomplish this result is clearly described by Krogh. "The arteries supplying a muscle branch freely and between the branches are very numerous anastomoses forming a primary net. The capillaries unite into venules intercolated between the arterioles, and the whole system of veins reproduces and follows almost exactly that of the arteries. All the veins down to the smallest branches are provided with valves allowing the blood to flow in the direction of the heart only. When the muscle contracts its form is greatly altered, the fibers become shorter and proportionately thicker. The blood is driven out by compression from a number of the venous branches and, when the muscle relaxes again, these can be filled from the peripheral end only. Since muscular contractions usually more or less regularly alternate with relaxations the system of valves makes of the veins of each muscle a very effective pump." The difference between arterial pressure and venous also sends the blood in the direction of the venules.

Thus the analogy of the role of adenylic in the enzymatic production of muscle energy and the increase of heart muscle energy coordinated with the regulation of vascular hemodynamics through dilatation of the coronary artery and increased peripheral vascular dilatation, can be carried still farther to the mechanism of venous return since the power of the myofibril to contract is also a function of the adenylic nucleotide. Thus the muscles provide a venopressor mechanism to meet the increased demands on the circulation created by the muscles themselves during periods of physical exertion. The improved return to the heart facilitates the more rapid output of the heart during active muscular effort. The cardiac output under exercise may be five times that at rest. Loss of muscle tone coupled with increased cardiac output would thus be one mechanism of circulatory failure. In shock and profound muscular relaxation this mechanism would prevail. The combatting of shock would thus call for increase of muscle work by the three mechanisms described above.

We will therefore have to consider first what is muscle contraction dependent upon and second what factors increase the capacity of a muscle to contract. Armed with a knowledge of these we would be in a better position to make some practical applications, since muscle contraction and relaxation become synonymous with muscle tonus and vitality.

Henderson suggests as measures for the indication of vitality and muscle tonus the following six procedures:

- (1) The resting oxygen consumption of the body.
- (2) The resting heat production.
- (3) The knee jerk and similar reflexes.
- (4) The intramuscular pressures that tend to induce the return of blood to the heart.
- (5) The electromyogram indicating the activity of the intramuscular booster pumps.
- (6) The volume of the venous return as shown by measurement of the height of the column of blood in the vein of an arm held vertically when the body is in the head down position.

The failure of these mechanisms results in "peripheral circulatory failure" for which Henderson has recommended the terms "hypotonia" and "tonic failure." His quotation from Shakespeare of the death of Falstaff as told by Mistress Pistol, nee Quickly gives a truly classical description of "peripheral circulatory failure."

"Nay, sure, he's not in hell: he's in Arthur's bosom, if ever man went to Arthur's bosom. A' made a finer end, an went away an it had been any christom child; a parted even just between twelve and one, even at the turning o' the tide: for after I saw him fumble with the sheets and play with flowers and smile upon his fingers' ends, I knew there was but one way; for his nose was as sharp as a pen, and a babbled of green fields. 'How now, Sir John,' quoth I: 'what man! be o' good cheer. So a' cried out "God, God, God! three or four times. Now I, to comfort him, bid him a' should not think of God; I hoped there was no need to trouble himself with any such thoughts yet. So a' bade me lay more clothes on his feet: I put my hand into the bed and felt them, and they were as cold as any stone: then I felt to his knees, and they were as cold as any stone, and so upward and upward, and all was as cold as any stone." The failure of tonus came with the loss of body heat and venous return, as well as the loss of the normal facial appearance.

In death venopressor failure follows directly on the failure of the spinal motor centers, progressing as the patient weakens. The loss of muscle tonus and the feeble beat of the muscle fibers means a failure of the booster pumps and diminishing amounts of blood are sent back to the right heart and thus less blood is available to be pumped into the arteries by the left heart. With the lessened arterial supply the vasomotor mechanism makes a compensatory effort to maintain adequate arterial pressure to supply blood to the brain. When compensation is no longer capable the ultimate drop of arterial pressure occurs and the circulation is at a stand still.

To Henderson must be credited the clear differentiation of the vasomotor and venopressor controls of the circulation. He quite rightly points out that ordinarily the adjustments necessary in our daily lives under the various degrees of stress and strain are met through the vasomotor nerves, both sympathetic

and parasympathetic as well as certain hormones which constrict and relax both arteries and veins. To this he adds a third mode of nervous control over the circulation in the venopressor mechanism. This latter mechanism depends on the spinal reflexes and the chemical adequacy of the muscle fibril. Just as the vasomotor system is interdependent on hormonal balance, so the venopressor system is related to the adenylic acid system. That all of the systems are integrated is obvious from the fact that the adenylic nucleotide also acts as a peripheral vasodilator and a dilator of the coronary artery.

One could grossly separate the differences in the adjustments in the circulation between the vasomotor and the venopressor by comparing the reactions to mental strain with those to muscular effort. Henderson recites the instance of his experiment at the age of 35 when he checked his own and his students' blood pressure before a difficult lecture and after. The students showed a rise of 20 mm. Hg. while his own pressure rose from 130 mm. before the lecture to 190 mm. at its end. He also noted that there was apparently no increase in oxygen consumption or respiration rate since he was not out of breath at the conclusion of the lecture.

In contrast with these vasomotor effects were the observations that Haggard and Henderson made on the members of a university rowing crew. After a training period the oxygen consumption was 10 times the resting amounts. Under the exertion of a boat race arterial pressure always rises, but certainly not because of any vasoconstriction; for, if there had not been considerable vasorelaxation, no vessels could have withstood the enormous volume of blood, probably 25-30 liters a minute, pumped into the arteries by the heart, and the same volume pumped into veins by the booster action of the powerfully working skeletal muscles. In this vasorelaxation lies one of the functions of the adenylic system which both supplies the energy and regulates the blood vessel size to meet the increased blood output.

It was this picture that led to the use of the iron salt of the adenylic nucleotide in essential hypertension with the clinical results here reported.

In hypertension the peripheral vessels are partly constricted with the myofibril of the blood vessel wall in a partially contracted state. I have shown that in the large voluntary muscles this spastic state is due to an inadequacy of energy available for relaxation with indefinite continuation of the partially contracted state. The mobilization of additional energy through treatment of the sympathetic supplemented by a supply of energy from the iron salt of adenylic nucleotide is sufficient to bring on relaxation of the myofibril of the blood vessel wall and lead to a drop in the diastolic pressure. As the diastolic comes down the systolic follows.

The typical reaction is as follows: First there is a slight rise in the systolic blood pressure and a lower-

ing of the diastolic giving an increased pulse pressure with increased capacity for work. The pulse rate increases, the peripheral vessels dilate producing a mild flushing of the skin that is quite generalized, usually more noticeable on the face. The hands and feet become warmer and the color of the nails reddens. After a few minutes the systolic falls progressively along with the diastolic so that a lower total level is established and the pulse pressure approaches a fairly normal output. During the first twenty four hours there is a gradual tendency to approach the initial blood pressure but not quite, so that the diastolic keeps lower than the initial height. Along with this comes a subjective feeling of relief of high blood pressure symptoms.

With the daily continuation of the injection of the iron adenyate comes a progressive approach to normal level usually within a week or ten days. In this procedure the iron adenyate is used alone, intramuscularly, and not mixed with any B complex since the peripheral vascular effect is greatest with the iron adenyate unreacted with the B complex amines as it is occasionally employed by some for the relief of fatigue and for enhancing B complex effectiveness. It is important also to avoid injecting into a vein since the peripheral vasodilator effect can be so sudden as to induce in rare instances syncope.

This approach to vasodilatation marks a radical departure from previous agents none of which are truly physiological in the sense that they occur normally in the body tissues to induce the desired hemodynamic effects. Katz, in a splendid article points out the lack of satisfactory agents for inducing adequate increase of coronary flow and heart muscle energy. One is also struck with the need of an agent that not only increases coronary circulation but supports the whole vascular mechanism. This fortunately appears to be nearing solution in the iron salt of the adenylic nucleotide (Ironyl).

Remarkably enough the improvement in peripheral circulation following upon the administration of iron adenyate is effective in stabilizing the blood pressure in low blood pressure cases as well. The improved muscle tonus and increased energy supplied to the heart muscle is sufficient to improve the cardiac output enough to bring a low blood pressure to normal levels.

A consideration of circulatory failure and hypertension must also take cognizance not only of the factors influencing the blood vessels from the outside but also the condition of the circulating fluid and inner wall of the vascular tree. Here too, it also will be seen that the nucleotides play a significant role. Knisely et al, in an important contribution to the understanding of circulatory factors described the pathologic appearance of "sludged blood" in a wide variety of pathologic states. By using binocular dissecting microscopes focused on obliquely illuminated bulbar conjunctival vessels of living unanesthetized, unoperated animals and men they were able to ob-

CLINICAL CASE RECORDS

Name	Age	Sex	History	Diagnosis	Inj. Date	B. P. Before Iron Adenylate (Ironyl)	10 Min. After	20 Min. After	30 Min. After	Reactions				
J. H.	36	M	Headaches with high blood pressure for last two years. For last six months unable to work. Has been treated by Dr. G. and Dr. F. intensively for essential hypertension and was finally advised to have cervical sympathectomy.	Essential Hypertension	4/6/48	200/120	170/110	170/110						
					4/7	165/100	148/95	170/108						
					4/8	178/118	155/95	150/100						
					4/9	160/110	140/90	155/100						
					4/10	170/105	160/105	160/105						
					4/11	170/110	170/110	180/120						
					4/12	170/110	145/100	158/100						
					4/13	155/110	170/105	158/108						
					4/14	160/100	130/90	160/115						
					4/15	155/105	150/98	158/100						
					A ten day interval was allowed and the injections again resumed. The patient went back to work after the first week of treatment and has continued working to date.									
					4/24/48	150/90	100/95	190/110						
					4/25	160/100	140/90	150/100						
N. L.	65	F	Severe frontal headaches radiating to back of head, especially in morning. Treated for hypertension in European Spas. Frequently had 240/210 systolic. Has been taking phenobarbital for several weeks.	Essential Hypertension	6/20/44	186/110	200/94	168/92		Relief of headache				
					6/21/44	received news of loss of brother-in-law	210/120	200/112	184/110	200/96	none			
					6/30/44	168/92	patient continued at this level for about 1 month, free from headache.			complete relief of headache				
M. F.	44	M	Headaches, nervousness and fatigability. Has been treated for high blood pressure for five years.	Essential Hypertension	6/26/44	192/144	198/144	186/134	168/120					
					6/27	188/122		170/130						
					6/28	164/122		186/136						
					6/30	178/122		176/116		Relief of symptoms				
					Patient continued to stay at this level without further treatment for six weeks, relatively free from symptoms.									
Gen. E. H.	74	M	Dizziness, nausea, high blood pressure.	Hypertension	1/6/48	188/98								
					1/9		168/98							
					1/12		158/96							
					1/16		152/88							
					1/19		148/76							
P. T.	40	F	Intermittent headaches, general tiredness for last few months.	Essential Hypertension	9/4/47	236/126	200/114	190/110	196/110					
					9/5/47	214/114	180/96	156/104	156/98	Relief of symptoms				
S. P.	38	F	Headaches, stiffness of muscles of neck and shoulder. Headaches awaken patient from sleep. Elevation of diastolic pressure induces symptoms. Four years duration.	Essential Hypertension	2/14/47	162/132	172/120	146/110		Relief of Headaches				
					Following a single injection patient would get relief of symptoms and would return from time to time on recurrence of elevated diastolic to secure relief.									
					9/4	160/109	172/128	176/130	156/116					
					9/5	162/114	150/104	156/100	148/98					
					9/6	164/112	170/114	156/112	148/102					
					9/11	Ironyl injections given by family physician for one week. Physician did not tabulate pressure readings.								
					9/20	160/114	150/102	156/104	156/100					
					9/27	142/102	156/98	156/98	146/96					
					Before diastolic pressure rises, patient complains of stiffness of muscles and cords of neck. This is followed by severe headache. Diastolic pressure always rises after these symptoms.									

Name	Age	Sex	History	Diagnosis	Inj. Date	B. P. Before Iron Adenylate (Ironyl)	10 Min. After	20 Min. After	30 Min. After	Reactions
R. M.	60	F	Headaches, dizziness and ear noises.	Hypertension	11/7/48	208/88	200/76	144/90	184/86	following tabulation by family physician.
					11/10	208/98	181/82	178/85		
					11/12	210/90	186/80	188/90		
					11/17	186/90	168/76	162/86		
					11/19	184/92	166/84	166/90		
					12/3	176/78	148/76	157/82		
					12/8	180/94	156/82	164/88		
					12/10	187/94	160/85	166/90		
Family Physician's comment: Mrs M. was not regular in her attendance, otherwise she might have shown a better result.										
F. K.	34	F	Recurrent headache, weakness, nausea, and vertigo.	Hypotonia	6/15/44	108/64	138/84			Relief of headache. Increased energy.
					6/19	120/88	120/86	120/82		
					6/22	114/78	118/88	120/76		
A. C.	53	M	Pain in left chest and shoulder in attacks since 1936. Hospitalized repeatedly for angina pectoris. Several attacks daily, very severe, takes nitroglycerine tablets every few hours for years.	Angina Pectoris Essential Hypertension	5/29/47	148/118	132/100	134/104	134/104	none had nucleotide reaction with flushing, perspiration, nausea (report of family physician). no reaction no reaction no reaction
					5/30	144/94	160/92	152/108	168/110	
					5/31	132/90	132/88	122/82	118/82	
					6/1	126/88	108/78	110/72	110/72	
					6/2	128/90	128/86	128/86	128/84	
					Injections and blood pressure readings from 5/30 to 6/2 were made by family physician.					
J. R.	48	M	High blood pressure for 15 years. Had many types of treatment, average range was 190/100 to 270/140, has headaches, dizziness and pounding in ears.	Essential Hypertension	6/17/44	174/104	188/110	180/108	178/94	relief of symptoms
					6/20	176/90	no treatment			
					6/26	150/106	168/98	156/88		
This patient received combined sphenopalatine ganglion treatment and iron adenylate.										
A. F.	47	F	High blood pressure with migraine headache on left side since childhood, worse in last five years. Some vomiting with vertigo and headache.	Essential Hypertension. Vascular migraine	4/16/47	178/134	200/140	172/128		Patient had complete relief of headache, dizziness and nausea and has had no recurrence of hypertension to date.
					4/18	178/122	188/130	172/110		
					4/22	192/120	192/122	188/98		
					4/24	182/110	168/96	168/104		
					5/26	178/114	150/94	150/96		
					6/9	178/114	150/88	146/88		
					6/10	156/98	124/76	120/76		
					6/11	126/80	124/76	120/76		
					6/12	148/108	148/84	150/82		
					6/13	150/90	140/76	142/82		
6/14	140/88	138/90	140/88							
K. W.	25	F	Severe chronic arthritis, generalized low blood pressure.	Low blood pressure hypotonia	6/13/44	112/76	120/80	148/78		increased energy response.
					6/17	114/68	120/88			
					6/22	116/74	122/80	120/80	122/80	
					6/26	116/72	120/78			

serve the movement of blood elements through the vessels.

In healthy, normal blood they found the circulating red cells were not agglutinated but tended to repel each other slightly. In carefully handled tissues red cell rouleaux were not present. No white cells or erythrocytes stuck to the inner surfaces of the walls of small vessels. The inner surfaces of the linings of normal small vessels were smooth and clean.

The flow of the unagglutinated blood was laminar or "streamlined" and in small arteries and veins the blood cells were in an axial stream and around them was a peripheral concentric layer of plasma. The wall of each lamina of this system consisted of unagglutinated blood cells, each layer was exactly one

red cell thick. This distribution is considered by Knisely to indicate the highest degree of good health. The rate of blood flow through each tissue of each organ of the body set the maximum rate at which the cells of that tissue can receive blood borne materials.

Any factors disturbing these conditions would impair not only oxygen supply but other nutrients as well. In addition to contributing important observations on the state of the arterioles Knisely showed that varying degrees of clumping or aggregation of blood cells occurs in a wide variety of disease states. Thus the blood was changed from its normal relatively fluid state to a circulating "sludge." By their means of study they were able to observe in human patients arterioles both temporarily and permanently plugged with masses of sludge and in some, short,

spindle shaped bulges (aneurysms) of arterioles. "In many patients large areas of the conjunctival vascular system, arterioles, capillaries and veins had been so tightly constricted that no red cells were visible or passed through sometimes for hours. The arterial blood pressure of many of these patients was taken. In all those listed it was within normal range or above. Further, these did not show evidences of increased venous pressure. Hence, the slow passage of this sludged blood through open vessels was directly due to the sizes and rigidities of the masses, not to increased venous pressure, failing venous return, or cardiac failure."

Knisely remarks that, "no severely ill person has yet been seen who did not have intravascular agglutination of the blood and visibly pathologic walls." This phenomenon is also commonly tested by the sedimentation rate introduced by Fahræas.

Bearing these elements in mind we see that there is another factor reducing oxygenation and leading to ischaemia of muscle. As the aggregation of the corpuscles occurs the opportunity for free gaseous exchange between corpuscles and plasma diminishes and the clumps themselves act as minute embolæ which may plug up small arterioles and capillaries or enter into the formation of thrombi. It has been pointed out that here may be a mechanism attacking the *vasa-vasorum* weakening blood vessel walls, and attacking multiple small areas of nervous tissue in the spinal cord and brain through nutritional obstruction. It is truly remarkable that in this mechanism of circulatory failure the nucleotides also play a role. Doyen showed many years ago that animal nucleic acid made up of the nucleotides, among which the adenylic nucleotide is the most active, diminishes the clotting of blood and in high dosage induces anaesthesia with failure of clotting for as high as 24 hours. This compares very favorably with heparin. Thus increasing the adenylic nucleotide level may play an important part in diminishing the sludging of blood. In practical experience I have found the sedimentation rate usually rapidly reduced after iron adenylate therapy.

The findings of Caspersson of the Karolinska Institute, Stockholm showed that the adenylic nucleotide level of mental cases, particularly schizophrenics and depressive psychoses was lowered. Improvement may be traceable to this aspect of improved nutrition to small areas of nerve tissue which followed attempts to increase the adenylic level.

Brown, Roll and Plentl studying the metabolism

of the adenylic nucleotide by inserting tracer elements into adenine found that after feeding the labeled adenine it could be found in the nucleic acid of cells as well as in the adenosine triphosphoric acid, A. T. P. of muscle. They thus showed that the adenine administered was utilized practically unchanged by the body cells both for growth and energy. They observed that the adenylic radical was more actively employed than that of the other nucleotides of nucleic acid.

SUMMARY

1. A new approach to the treatment of circulatory failure and hypertension based on the biochemistry of the myofibril is presented. The stage of muscular contraction is shown to be the expenditure of energy. Relaxation requires a fresh supply of energy. Muscle spasm whether it affects the large muscles, heart or small blood vessels is an energy poor state so that contraction may persist until energy is supplied by the administration of the energy rich phosphate bond in the adenylic nucleotide.

2. Essential hypertension is a result of contraction of the peripheral vessels and may be relieved by supplying the necessary energy for relaxation by the administration of iron adenylate (Ironyl).

3. Circulatory failure is ultimately related to failure of venous pressure incident to loss of muscle tonus. Muscle tonus is dependent not only on the normal maintenance of nerve impulses from the spinal cord but also on biochemical adequacy of the myofibril, the contractile elements of which are made up of actin, myosin and adenosine triphosphate (A. T. P.) and inorganic elements, chiefly calcium and magnesium.

4. The adenylic nucleotide system, A. T. P. — A. D. P. — A. M. P., not only supplies the only known source of muscle energy but also regulates the hemodynamics of the body. The adenylic nucleotide affects general muscle tonus as well as heart muscle tonus, dilates the coronary and peripheral blood vessels, stimulates blood formation and reduces the sedimentation rate.

5. The iron salt of the adenylic nucleotide has proven clinically effective as a new aid in circulatory failure and in hypertension.

6. A new conception of hypertension based on the energy poor state of the myofibril in contraction is presented and a new therapeutic approach through the adenylic nucleotide is suggested.

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The Effect of Tripelennamine Hydrochloride (Pyribenzamine) on the Gastric Acidity of Patients with Peptic Ulcer

By

SEYMOUR A. HARTMAN, M.D.

and

DONALD M. MOORE, M.D.

SALT LAKE CITY, UTAH

INTRODUCTION

SINCE EDKINS' (1) DISCOVERY that an extract from pyloric mucosa had a powerful stimulating effect on gastric secretion when injected intravenously, it has been amply demonstrated that the active principle in these pyloric extracts is histamine (2). Whether or not histamine is identical with the gastric hormone which is liberated into the blood when food enters the stomach has not been settled. Portis (3) states, however, that histamine is apparently the gastric hormone. Edkins and Tweedy (4) have named the active principle from pyloric extracts gastrin.

Pyribenzamine has been shown to be a powerful antihistaminic. In appropriate doses it prevents asthma and convulsions in guinea pigs to which histamine has been given intravenously (5, 6, 7). Feinberg (8) has stated in a review of the subject of the antihistamine compounds that these substances seem to act by competing with histamine for attachment to the receptor cell.

From the Medical Service, Veteran's Administration Hospital, and the Department of Medicine, University of Utah Medical School, Salt Lake City, Utah.

McGavack, Elias and Boyd (9, 10, 11) have described the effect of dimethylaminoethyl benzhydryl ether hydrochloride (Benadryl) upon gastric acidity in three separate papers. During their study of the pharmacologic properties of benadryl on subjects without organic gastrointestinal pathology, they noted a marked decrease in the free and combined acids in the stomach of patients receiving Benadryl. While on Benadryl, their subjects were refractory even to the administration of histamine. In most of their subjects they noted a maximal effect on the gastric acidity between the first and second week on Benadryl. They also stated that within a few days after the administration of Benadryl was discontinued, the fasting and combined acids returned to normal.

Crane, Lindsey and Dailey (12) attempted to prevent histamine induced ulcers in guinea pigs with the administration of Benadryl. They administered 135 mg./Kg. of body weight daily of Benadryl in divided doses five times daily by the intraperitoneal route. They found no significant difference in the incidence of ulcers or perforations in the treated and the control animals.

In view of the above work, it seemed theoretically sound to proceed with the administration of pyribenzamine in relatively large doses to patients having peptic ulcers with symptoms. Pyribenzamine was chosen because of the low incidence of side reactions reported with its use (13).

PROCEDURE

During a one month period, alternate patients admitted with the tentative diagnosis of peptic ulcer were placed on pyribenzamine in doses of 100 mg. given three times daily after meals. A total of 12 patients were studied. Both the control group and the group receiving pyribenzamine were placed on a progressive Sippy-type diet. In addition, the controls received fifteen cc. of Amphogel every hour during the day.

Gastric analysis was performed in the morning on an empty stomach on all subjects. The fasting juice was aspirated and this was followed by the administration of 50 cc. of 7% alcohol through the Levin tube. The stomach was emptied every fifteen minutes until five samples had been obtained. Then one milligram of histamine diphosphate (containing 0.368 mg. histamine base) was administered subcutaneously and the last sample withdrawn one half-hour later. Gastric analyses were performed at approximately weekly intervals. All patients were subjected to gastrointestinal series by X-ray and gastroscopic examinations were performed when indicated.

Later in the course of our study, in some of the subjects the dosage of pyribenzamine was increased to 100 mg. given four times daily. The time of administration was changed so that the patients received

their first dose of pyribenzamine at 6:00 a. m. even on the morning in which gastric analysis was to be performed.

Two of our series did not have an ulcer on X-ray. Their admission histories were only suggestive of an ulcer. One of these patients fell into our control group and the other into the group receiving pyribenzamine.

RESULTS

Figure I shows the results of gastric analyses on E. B., a 31-year old white male clerk with a one year history of epigastric complaints. Gastrointestinal series revealed a characteristic ulcer deformity of the duodenal bulb and on fluoroscopy an ulcer crater was demonstrated. He improved symptomatically on the progressive Sippy-type diet, and pyribenzamine given in 100 mg. doses three times daily. However, there were no significant changes in his fasting free or total acid nor in his response to the alcohol meal and histamine.

Figure II was obtained from the gastric analyses on M. E., a 54-year old white male carpenter with a two year history of epigastric discomfort. GI series revealed a persistent deformity of the duodenal bulb. No crater could be demonstrated. The patient showed symptomatic improvement on the Sippy diet and pyribenzamine in the routine dosage. No significant changes were noted in his fasting values nor after the administration of histamine.

Figure III represents the curves obtained on C. S., a 31-year old white male mechanic with a 2 1/2-year story of epigastric distress. On GI series he had both a deformed duodenal bulb and an ulcer niche in the greater curvature of the bulb. He was

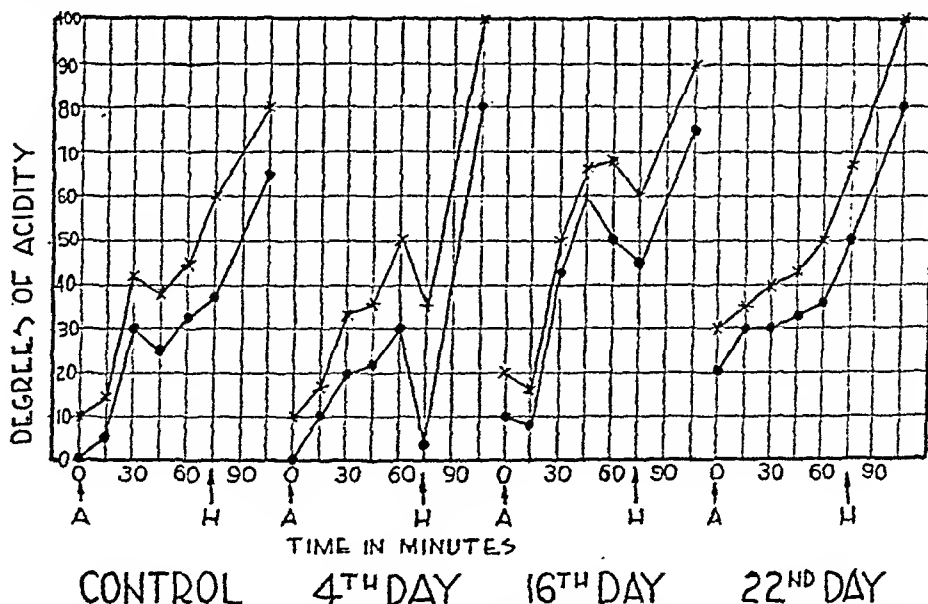


Fig. 1. — E. B. Duodenal Ulcer. x x represents total acidity. • • represents free acid. The curve labelled Control was obtained before any therapy was instituted. Gastric aspirations were done at the intervals indicated. A indicates the time of administration of the alcohol meal and H indicates the time of injection of 1.0 mgm. histamine diphosphate.

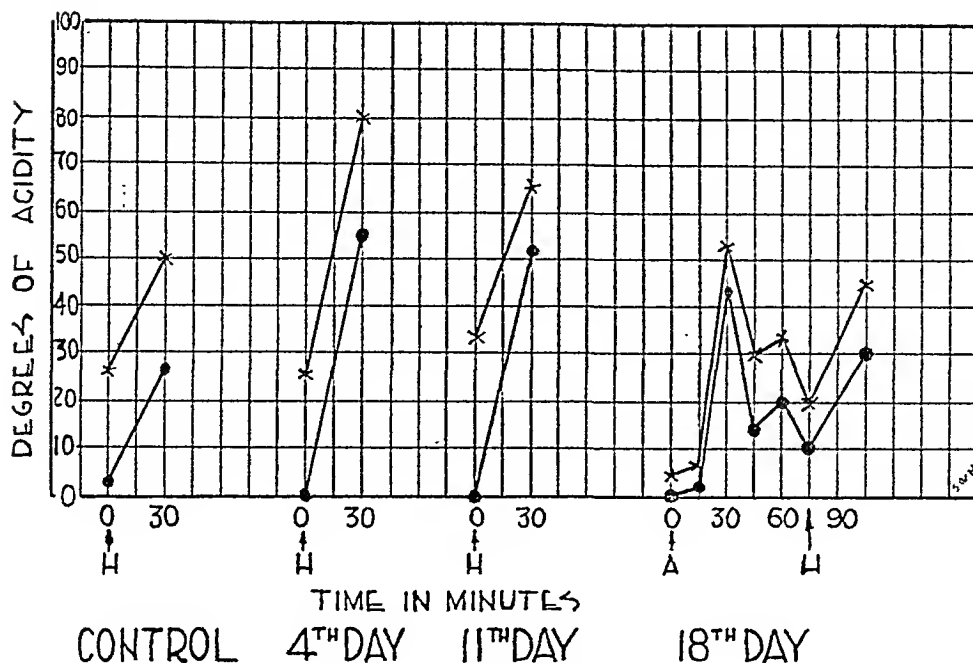


Fig. 2. — M. E. Duodenal Ulcer.

placed on pyribenzamine in the routine dosage plus the progressive Sippy diet. Symptomatic improvement was satisfactory. There was no significant change in his acid responses.

Figure IV shows the results of the gastric analyses on G. O., a 27-year old white welder with a two-year history of epigastric pain typical of peptic ulcer. Two consecutive gastro-intestinal series revealed a persistent defect in the pre-pyloric area at the lesser curvature. It was stated that this appearance was compatible with an ulcer crater. The lesion was not visible by gastroscopy. The patient's symptoms improved on a progressive Sippy regimen with 100 mg. py-

ribenzamine given t. i. d. His gastric analyses showed no significant lowering of free or total acid despite his symptomatic improvement.

Figure V reveals the gastric acidity curves obtained on R. R., a 40-year old white male cowboy who had a five-year ulcer history. On June 10, 1947, he had a gastroenterostomy and a vagotomy with improvement lasting about two months. Gastrointestinal series revealed a gastroenterostomy with a widely patent stoma. A persistent deformity of the duodenal bulb was visualized. Gastroscopy revealed the characteristic picture of chronic hypertrophic gastritis. There was no significant response to pyribenzamine in either

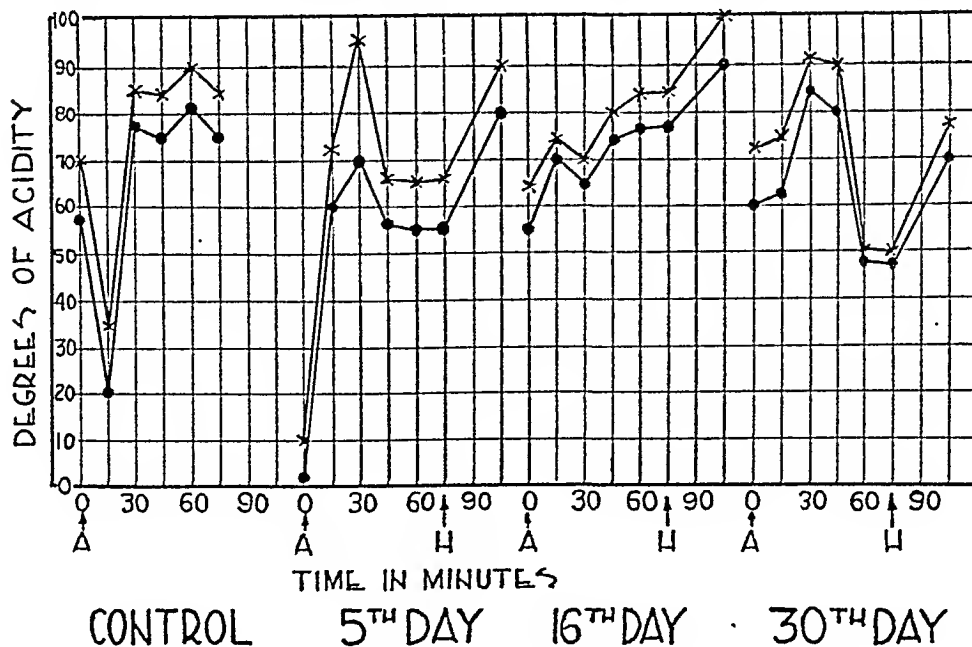


Fig. 3. C. S. Duodenal Ulcer.

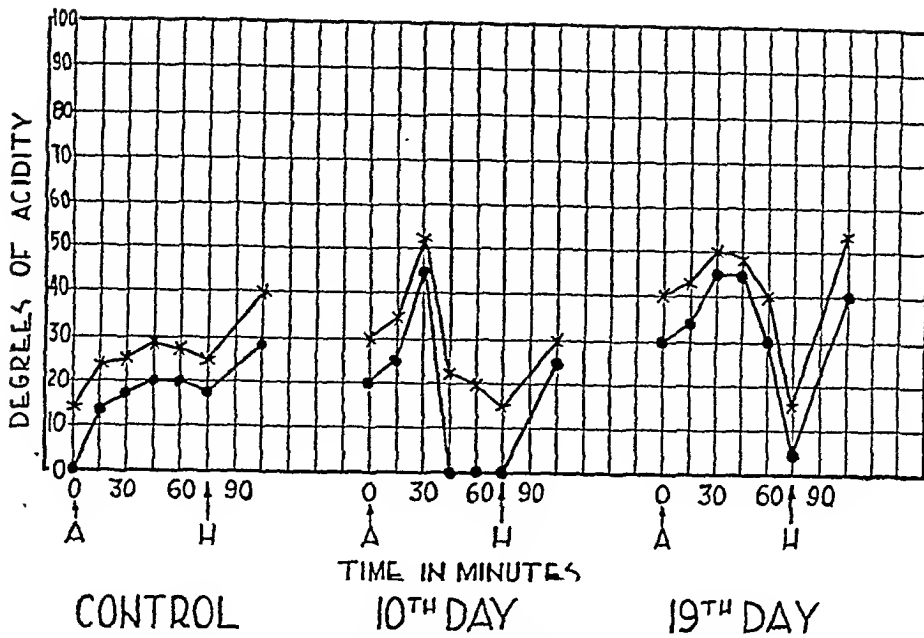


Fig. 4. — G. O. Gastric Ulcer

the 100 mg. dosage three times daily nor in the 100 mg. dosage four times daily. He did respond symptomatically while in the hospital on his Sippy-type diet.

Five patients with demonstrable ulcer craters on X-ray served as controls. They received the Sippy-type diet with the addition of Amphogel. The results of their gastric analyses did not vary significantly during a 30-day course of therapy. Their fasting acid values did not change during their course despite symptomatic improvement in all four patients. One patient who had no demonstrable lesion on X-ray and who did not have a convincing history for peptic ulcer was placed on pyribenzamine. During a five-week follow-up, his gastric juice showed no change in any of the test meals. He continued to have symptoms.

No significant change in the volume of gastric secretions was noted in any of the subjects. No serious reactions to pyribenzamine were encountered.

After the completion of this study, it was decided to test the effect of Benadryl on the gastric acidity of patients with peptic ulcer. Benadryl given in the dosage of 300-400 mg. daily in divided doses has had no effect on the gastric acidity of two patients with duodenal ulcers followed for four weeks.

CONCLUSIONS

Tripelennamine hydrochloride (pyribenzamine) has no significant effect either on the volume or the degree of acidity of the gastric juice in patients with peptic ulcer.

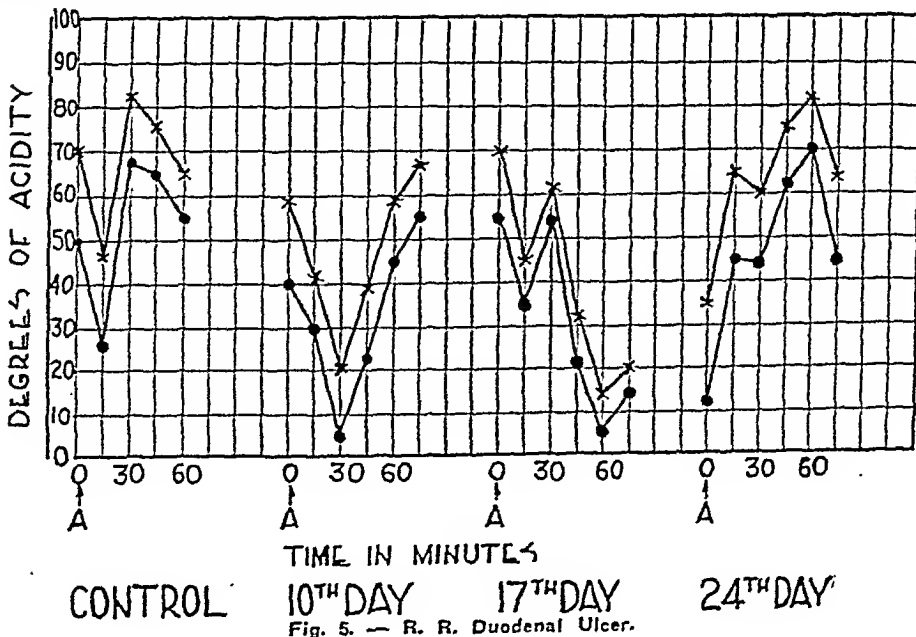


Fig. 5. — R. R. Duodenal Ulcer.

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NUTRITION

Vitamins and Hormones in Nutrition

IV. Gastro-Intestinal Disease and Reduced Dietary Intake

By

BENJAMIN F. SIEVE, M.D.

BOSTON, MASS.

THE SYNERGISTIC ACTIVITY of vitamins and hormones in nutrition, and the etiological significance of endocrine dyscrasia and infection in nutritional deficiencies were discussed in the first three reports in this series (1-3). Conclusions were based on observations in 200 patients with nutritional disorders. In this communication, the fourth in the series, we consider two more etiological factors, namely gastro-intestinal diseases and reduced dietary intake, which were present in 134 cases, 67 per cent of the total series. In many cases they occurred in combination with other predisposing factors, as mentioned in the original paper (1) and analyzed in Chart I. Gastro-intestinal disease was found in 81 cases, 40.5 per cent. and reduced dietary intake in 53 cases, 26.5 per cent. These two groups are so closely related, and so often interchangeable, that it seems best to review them together.

Gastro-intestinal diseases, generally speaking, are due either firstly to pathological changes involving specific localized portions of the gastro-intestinal tract, or secondly to changes following systemic infection which may involve any part or even the entire gastro-intestinal canal. Among the more common diseases of the first group are appendicitis, gastric and duodenal ulcer, cholecystitis, cholelithiasis, and intrinsic or extrinsic obstructions. They are clinically diagnosed with relative ease. On the other hand, secondary changes, or referred gastro-intestinal symptoms are sometimes complicated and confusing. They may result from such primary conditions as pulmonary tuberculosis, chronic glomerular nephritis, acute plumbism, or "old fashioned bellyache." But whether we are dealing with a primary specific disease such as chronic diverticulitis, or a secondary disease such as mucous colitis, we must regard them in the light of entities capable of initiating a chain of reactions which may eventually lead to the disruption of the synergistic action of vitamins and hormones.

* Junior Visiting Physician, Boston City Hospital.

* Instructor in Medicine, Tufts College Medical School.

* Resigned, December 1946.

Reduced dietary intake may, of course, accompany or follow any of the major gastro-intestinal diseases, but it may also result from psychological disturbances or minor pathological lesions which are frequently overlooked. To list a few of these we can mention sore tongue, painful gums, carious teeth, infected tonsils and sinuses, faulty eating habits, emotional instability, and food phobias, all of which can play an important role in nutritional derangement by interfering with proper food intake.

Patients with abscessed teeth, malocclusions, missing teeth, and ill-fitting dentures should be referred to dentists for the cure or correction of these conditions. Dental surgeons, orthodontists and prosthodontists recognize that in order to maintain good nutrition and health the bite should be as nearly mechanically perfect as possible. Painful infected teeth, sore gums, and ill-fitting dentures interfere with appetite and mastication of food. Patients who develop mechanical abnormalities or oral pathology, are unable to chew their food adequately, and therefore are apt to substitute with semi-solid or liquid foods. They commonly eliminate meats, vegetables, and other important foods. Thus they not only partake of a limited amount of food, but interfere with the dietary balance necessary to avoid deficiency states.

Food phobias and fixed faulty eating habits have been found to be of considerable significance as an etiologic clue in many of the cases of nutritional deficiency caused by reduced dietary intake. We frequently see individuals who develop idiosyncrasies and distastes as regards certain articles of food, and other persons who actually fear to eat given kinds of food. It is therefore not surprising that some of these people eventually suffer from nutritional deficiencies for which they seek medical advice. A case in point is a woman in her sixth decade who presented just such a nutritional picture. She told an interesting story. When she was a little girl her superstitious grandmother admonished her never to eat tomatoes, of which she had been very fond, because they caused cancer. This incident so deeply impressed the patient that she developed a phobia not only against tomatoes, but against all red, soft, or seedy foods. Ultimately she had omitted from her diet all red vegetables and fruits, red meat, red jellies, candies and ices, and practically all fruits containing seeds. With this history, which covered a fifty year period, it was not difficult to understand why the patient was undernourished, and had myriad complaints and symptoms consistent with a vitamin-hormone dyscrasia.

One of the most common phobias which can lead to faulty food intake is the fancied inability of a patient to swallow pills or capsules. Every practitioner must at some time have been confronted by the patient who says, "I must have liquid medication, Doctor, because I just cannot swallow a pill." This same fixed belief frequently extends to imaginary difficulty in swallowing certain types of food and their subsequent elimination from the diet, thereby leading to faulty dietary intake and resultant nutritional

imbalance. Correction of food, pill, and capsule phobias has permitted the establishment of a well balanced adequate diet, and has frequently helped to overcome concurrent psychogenic disturbances.

The existence of food phobias, peculiar eating habits, minor pathological lesions or malocclusions must be recognized if deficiency cases of this nature are to be treated at their sources. Only by means of a detailed, carefully analysed history can such underlying conditions, which may have existed for years, be disclosed. If a story of insufficient food, wrong foods, or unbalanced diets, especially associated with gastro-intestinal symptoms, is obtained, a thorough physical examination including pertinent laboratory tests will complete the data necessary to reveal the causes and effects of the nutritional deficiency. Rarely does such a patient fail to reveal concomitant hormonal and vitamin deficiencies, because hormones and vitamins cannot be effectively utilized when there is a limited food intake or faulty digestion.

Six cases have been chosen for discussion. Disruption of the physiological synergistic action of vitamins and hormones in gastro-intestinal diseases is demonstrated in the following three cases. These will be followed by three cases illustrating the effect of faulty food intake.

GASTRO-INTESTINAL DISEASE

Case 1. The first case is that of a 41 year old, married, white male, whose chief complaints were gastro-intestinal distress, with gas and some pain, of fifteen years' duration, and fatigue and malaise of ten years' duration. The patient himself stated that he could remember no period since he was 12 years old when he had been entirely free from "stomach complaints." X-rays of the gastro-intestinal tract taken elsewhere at the onset of symptoms had been negative, and provisional diagnoses of "gastro-intestinal disease" and chronic cholecystitis were made. The patient had been placed on a low fat diet, which later was further restricted by an ulcer diet, so that actually his diet became a combination of the two. Not only did he avoid fats and splees, but he omitted practically all green and yellow vegetables and all fruits except cooked prunes. Two or three years after starting this diet he developed severe gingivitis and pyorrhea, necessitating the extraction of most of his teeth, and resulting in the usual complications attendant upon adjustment to dentures. Weight loss had been slight, but symptoms such as constipation, distention, pyrosis, pain, and gastric distress became increasingly persistent. Five years prior to consultation vague joint pains, paresthesias, and severe occipital headaches began to develop. For a period of about eighteen months he had noted mild prostatic symptoms, with dribbling, decreased pressure of the stream, and nocturia. During the same period nervousness, irritability, and fatigue became more pronounced, and he noted a moderate decrease in libido. Over the entire fifteen year period since the onset of his first complaints, numerous medications had been given to the patient, all directed toward his gastro-intestinal symptoms, and affording him little relief.

Physical examination revealed a well developed, fairly well nourished male. The hair was dry and lusterless, and the scalp was scaly. There was two plus edema of the upper and lower eyelids. The nasal septum was deviated slightly to the left, and the inferior turbinates were somewhat hypertrophied. There were fine leukoplakia on the hard palate. He wore complete dentures. The gums showed

some areas of sponginess. The tongue was slightly coated, the lingual papillae were markedly atrophic at the tip and along the lateral borders, and there was redness and glistening of the pellagrous type. The pharynx showed considerable redness and follicular changes. There were slight beginning cystic changes in the left breast. The heart was moderately enlarged. Cardiac rate was 60, and the rhythm regular. Blood pressure was 86 systolic, 58 diastolic at its highest level after coffee. The lungs were essentially negative except for rare rhonchi at the left base after cough. Palpation of the abdomen was essentially negative except for the liver, which was palpable two finger breadths below the right costal margin, smooth, with slight tenderness on deep palpation in the region of the gallbladder. There was a small umbilical hernia. Rectal examination revealed thickening and superficial fissuring of the perianal epidermis and anal mucous membrane, and tiny internal nonthrombotic hemorrhoids. The prostate was moderately hypertrophied, the median sulcus was not palpable, and there were no nodules. There were changes in the joints consistent with both infectious and hypertrophic arthritis. The skin showed areas of thickening and drying, and a slight papular eruption. The hands and feet were cold to palpation. There was slight pitting edema of the lower extremities. Dorsalis pedis and posterior tibial vessels were palpable but sluggish, particularly on the left. The nails were ridged and brittle.

Laboratory data were within normal limits. Basal metabolic rate was minus 16 per cent, and total proteins in the blood were definitely low.

The patient was placed on a full diet, and a regime of complete substitution therapy, oral and parenteral, was outlined for him. Oral medications consisted of thyroid extract, an elixir of the whole vitamin B complex, vitamins A, D, C, with minerals, diethylstilbestrol, and hydrolyzed proteins.* Parenteral therapy consisted of the anterior pituitary like hormone, α -estradiol benzoate, testosterone propionate, thiamine chloride, liver extract, and the whole vitamin B complex with ascorbic acid. Prostatic massages were given once a week.

After being under this therapeutic regime for two months there was frank improvement in the patient's condition, and gradual disappearance of his major complaints. He was entirely free from pain and pyrosis, had practically no gastric distress, and only occasional gas. In spite of the fact that he had taken many fruits, vegetables, meats, and fats, which he had avoided for many years. His appetite was good, and he showed a slight gain in weight. He was much more energetic, did not fatigue as easily, and had been much less irritable. He had noticed practically no joint pain. Prostatic symptoms had disappeared, and libido was definitely improved.

Physical findings at check-up examination two months after the beginning of therapy revealed considerable improvement. The hair was more moist and of better luster. Edema of the eyelids had subsided. The leukoplakia of the mucous membranes and hard palate had practically disappeared. Lingual papillae were more pronounced. Heart measurements were nearly normal. Blood pressure was 116 systolic, 74 diastolic. There was greater expansion of the lungs, and no pathology was found. The liver edge was barely palpable, and there was no tenderness nor spasm. Rectal examination revealed less perianal thick-

ening, and no fissures. The prostate was smaller. The skin was more moist and of better tone. The joints were more freely movable, and there was less crepitus. Pitting edema of the lower extremities had entirely disappeared, and the hands and feet were much warmer. The nails were firmer and less ridged.

Laboratory data were at high normal levels. Basal metabolic rate was plus 4 per cent, and total blood proteins were within normal limits.

At this time the therapeutic regime was modified by the addition of whole liver capsules* containing added factors of the vitamin B complex, and the lipoids of the liver; adjustment of parenteral therapy to less frequent intervals, and reduction of prostatic massages to once bi-weekly. This adjusted regime was followed for a three month period at the end of which parenteral therapy and prostatic massages were omitted entirely. For the past fifteen months this patient has been maintained at optimal levels on a well balanced diet and oral medications alone, with essentially no recurrence of subjective symptoms.

COMMENT

The significance of gastro-intestinal disease and reduced dietary intake as etiological factors in nutritional disorders and impaired synergistic activity of vitamins and hormones is well illustrated in this first case. Over a period of years, as we have seen, this patient's food intake was radically reduced. The low fat diet, in itself restrictive, was further limited by the ulcer regime, and extraction of the teeth followed by a long period of adjustment to new dentures constituted the final step in producing a very deficient diet. At this point not only were fats, spices, many vegetables and fruits omitted because of dietary restrictions, but only soft and semi-solid foods could be eaten because of the dental condition. All of this took place between the ages of 26 to 41, the patient's most active productive years. The resultant nutritional deficiency complicated an apparent hypothyroid condition which had probably been present since puberty. The entire syndrome was further complicated because of the hepatic and prostatic infection. We meet again our frequently encountered triad of the male climacteric, as mentioned repeatedly in previously publications (1, 14): endocrine dyscrasia, nutritional imbalance, and infection. In this patient avitaminosis and hypoproteinemia were particularly marked.

Perhaps the most striking feature of this case is the therapeutic demonstration of the necessity of

* Material supplied through the courtesy of Rawl Chemists, New York 3, New York. Trade name "Rawl Whole Liver Vitamin B Complex Capsules." Each capsule contains 0.5 Gm. of desiccated whole liver (equivalent to 2.5 Gm. of fresh whole liver) and provides: Vitamin B complex factors: thiamine (B1) 1.0 mg., riboflavin (B2) 2.0 mg., niacinamide 5.0 mg., choline chloride 12.0 mg., pyridoxine (B6) 0.2 mg., ca. pantothenate 0.2 mg., inositol 5.0 mg., biotin 0.6 mg., folic acid 10.0 mcg. Amino acids: methionine 11.0 mg., arginine 19.0 mg., cystine 4.0 mg., glutamic acid 37.5 mg., histidine 5.5 mg., isoleucine 18.5 mg., leucine 27.5 mg., lysine 16.5 mg., phenylalanine 10.5 mg., threonine 11.0 mg., tryptophan 2.5 mg., tyrosine 10.0 mg., valine 17.0 mg. The whole liver substance used in this preparation contains all the lipid and water-soluble B complex factors as found in fresh whole liver.

* Material supplied through the courtesy of Dr. Gustav J. Martin, The National Drug Company, Philadelphia, Pennsylvania. Trade name "Aminonut Powder." Protein hydrolysate "National" containing amino acids. Protein hydrolysate "National" 94 per cent; sodium chloride 2 per cent; flavoring agents 4 per cent. Total protein (N x 6.25) approximately 70 per cent. Amino acids (amino acid N x 6.25): 40 per cent. Each ounce contains 20 Gm. of protein, and 12 Gm. amino acids.

considering the patient as a whole, rather than focusing attention on an isolated anatomical site or system. Although the diagnosis of gastro-intestinal disease and cholecystitis had been made at the onset of his illness, therapy had been directed only to the symptoms produced by these conditions. In cases such as this treatment of the gastro-intestinal pathology per se is of little value, treatment is necessary for the entire body. Complete oral and parenteral substitution therapy for the hormone dyscrasia and avitaminosis, plus eradication of infection are all essential for maximum restoration of physiological balance and health.

Case 2. The second case is that of a 37 year old, white, unmarried female school teacher, who complained of extreme fatigue, and persistent "colitis," manifested by abdominal cramps and diarrhea, over a five year period. At the onset of symptoms her condition had been diagnosed elsewhere as "mucous colitis." Stool examinations had been negative for the usual pathogenic organisms. A bland diet had been prescribed, and had afforded her some relief, but the attacks of "colitis" persisted. She had come to attribute all of her symptoms to the "colitis." Appendectomy had been performed five years before. Menstrual periods were normal except for premenstrual tension, irritability, depression, and some breast fullness. For some years she had noted increased nervousness, insomnia, some joint pains, and the appearance on the skin of an increasing number of brownish spots. She complained also of headaches, and had observed increased dryness of the hair and skin, and brittleness of the nails. With the onset of the colitis the loss in weight had been severe, reaching a low level of 89 pounds, which had been only partially regained. During the year prior to consultation fatigue had become more pronounced, and she began to have some flushes, periods of depression, and crying spells.

Physical examination revealed a thin, well developed, and poorly nourished female. The hair was dry and lusterless, with some achromotrichia. The scalp was very dry. There was two plus edema of the eyelids, conjunctivae were pale, and sclerae injected. The lips and mucous membranes were pale. Clusters of leukoplakia studded the mucous membranes. There was some recession and sponginess of the gums. The tongue was slightly coated, and there was a slight tremor. The lingual papillae were atrophic at the tip and along the borders. Pharynx showed some follicular hypertrophy, and the tonsils were slightly enlarged and cryptic. The thyroid was smooth and enlarged, more marked on the right. There was some thickening through Cooper's ducts in the left breast. The heart was moderately enlarged, the sounds of good quality, regular. Blood pressure was 128 systolic, 64 diastolic. There was some coggwheel breathing at the apex of the right lung with an occasional fine crepitant rale after cough. The abdomen was slightly distended, and the liver was palpable two and a half finger breadths below the right costal margin. It was smooth and there was moderate tenderness in the region of the gallbladder. There was tenderness with slight spasm over the entire colon. Pelvic examination revealed moderate atrophic changes of the vaginal mucosa, a small erosion of the cervix, and some mucous discharge. Rectal examination revealed a markedly spastic sphincter muscle, edema and hyperemia of the rectal mucosa. The skin was extremely dry, of poor tone, and there were numerous fine, verrucous, brown pigmented nevi. There was some crepitus in the larger joints. The extremities were cold. Fingernails and toenails were brittle and thickened. Reflexes were hyperactive, but none were pathological.

Laboratory data were at somewhat low levels. Basal metabolic rate was minus 5 per cent. Fasting nonprotein nitrogen was 43 mg. per 100 cc. of blood. Sputum test

for acid-fast bacilli was negative. X-ray examination of the chest was negative. A gastro-intestinal series was negative except for hypermotility.

From the examination, and experience with similar cases, we were convinced that the "colitis" was merely a symptom of the general condition of nutritional, vitamin, and hormone deficiencies. Therefore the following therapy was given. A well balanced diet was prescribed which included raw and cooked vegetables. Complete substitution therapy was administered orally and parenterally. Oral medications consisted of thyroid extract, α -estradiol, para-aminobenzoic acid, and an elixir of the whole vitamin B complex. Parenteral therapy included α -estradiol benzoate, thiamine chloride, the anterior pituitary like factor, and corpus luteum hormone.

At the end of one month there was considerable general improvement, with subsidence of the abdominal and other subjective complaints. Physical and laboratory data obtained at check-up examination corresponded with this improvement. Complete oral and parenteral therapy was continued as previously outlined, but to the parenteral therapy was added mono-ethanolamine para-aminobenzoic acid, whole liver extract, and the whole vitamin B complex intravenously. Banana powder was added to the oral medications.

The patient followed this augmented regime for eight months. Her general condition continued to show improvement. There was no recurrence of the "colitis." Premenstrual tension and irritability completely disappeared, and she was no longer subject to the extreme fatigue of which she had previously complained. She gained 4 1/2 pounds.

At physical examination at this time the hair was more moist and of better luster. There was no edema of the eyelids; conjunctivae and sclerae were clear. Lips and mucous membranes were moist, of good color, and there were no leukoplakia. The gums were firm. The tongue was slightly coated, there was no tremor, and the lingual papillae were well pronounced. The thyroid was smaller. The pharynx showed improvement, the tonsils remained the same. Slight fullness persisted through Cooper's ducts in the left breast. Heart measurements were nearly normal. Blood pressure was 110 systolic, 70 diastolic. The lungs were clear. There was no distention of the abdomen. The liver was barely palpable at the right costal margin, and there was no tenderness over the gallbladder. Tenderness and spasm over the colon was not elicited. The vaginal mucosa was more normal, the cervix was well healed, and there was only slight mucous discharge. Rectal examination showed a marked decrease in sphincter spasm, edema and hyperemia had entirely cleared. The skin was more moist and of better tone, several of the pigmented nevi had disappeared, and the others were lighter in color. The joints were more freely moveable, with less crepitus in the larger joints. Extremities were warmer, and the nails were firmer. Reflexes were normal.

Laboratory data were at optimal levels. Basal metabolic rate was plus 3 per cent. Fasting nonprotein nitrogen was 31 mg. per 100 cc. of blood.

COMMENT

This case presents a problem in vitamin-hormone deficiencies, wherein the gastro-intestinal tract was the apparent source of major distress. Yet actually it was unjustly incriminated, serving merely as the scape-goat in a general physiological imbalance. As evidenced by the history and physical examination, the "colitis" was merely one symptom in the syndrome, or the culmination of a whole chain of events. Their sequence can be reconstructed easily: first moderate glandular imbalance; then mild infection; then

interference in food metabolism with faulty absorption of the vitamins; then, with the beginning of the climacteric, further hormonal imbalance; then tissue irritation affecting the nervous system and cell metabolism; and finally an upset of the gastro-intestinal tract resulting in the appearance of mucous diarrhea. Severe involvement of the sympathetic nervous system was evidenced by flushes, irritability, depression and crying spells. Proper diet, removal of some of the foci of infection, and complete replacement therapy for a sufficiently long period resulted in complete relief of symptoms, and the elimination of the so-called colitis. It will be noted that the infected tonsils were not removed. Apparently, however, clearing of infection in the liver, gallbladder, cervix and rectum resulted in such marked reduction of the total body infection that the tonsils, no longer activated by these other foci, became merely a non-infectious focus.

In view of the foregoing analysis it may be considered that this case was improperly classified as one in which gastro-intestinal disease was the chief predisposing factor. All previous treatment had been centered around the gastro-intestinal upset, and had been directed solely to relief of the colitis without avail. Moreover, although slight hormone and vitamin imbalance had been present for many years, it was not until the appearance of the acute gastro-intestinal symptoms that severe impairment of the vitamin-hormone balance occurred. With this in mind we can correctly classify this as a case of functional gastro-intestinal disease.

This case should serve as a striking example of the necessity for careful study of each individual patient in order to determine the true etiological factors, and to initiate proper therapy. This patient had been told that she had "colitis," and had so used this specific term to describe her chief symptoms, rather than the simpler "cramps and diarrhea." "Colitis" seems to have become a handy waste-basket diagnostic term wherever, in a given case, cramps and frequent loose movements are prominent symptoms. If, under the usual symptomatic treatment, the condition does not subside, such patients are frequently and unfortunately apt to be classified as psychoneurotic, or by similar terms. Detailed study at the onset of the illness will often reveal the etiology of the condition as merely a symptom of the vitamin-hormone deficiency syndrome. When classified as such, substitution therapy usually corrects this common functional gastro-intestinal disorder.

Case 3. The third case is that of a 33 year old, unmarried female, whose chief complaints were fatigue and exhaustion of five years' duration. Her past history revealed esophagitis at age 12, as a complication of typhoid fever, which incapacitated the patient for eighteen months. At age 23 she began to have recurrent attacks of sharp spastic pain on the right side of the abdomen, apparently aggravated by certain foods. These attacks continued over the next five years, with increasing frequency and severity, and after that they took place once or twice a week, accompanied by diarrhea, nausea, and vomiting, interspersed with periods of constipation. She was rarely free from gas and pain, and gradually lost weight and

strength. She also developed unsteadiness in gait, multiple dental caries, intermittent aching in the bones and joints, edema of the fingers, dyspnea, palpitation, muscular weakness, excessive perspiration, and extreme nervousness. During the entire ten year period since the onset of her illness, the patient disclosed a long history of emotional strain, family discord, and financial difficulties. By profession the patient was a silversmith, but because of her ill health, had done no work for several months. She had been treated elsewhere, but apparently without relief.

Physical examination revealed a thin, well developed and poorly nourished female. The head was negative except for a slight depression above the occipital lobe. The hair was dry, lusterless, with early achromotrichia. The scalp was dry. There was retraction of the right ear drum from an old perforation. The eyelids were edematous. Eye movements were normal except for slight rotary nystagmus. Ophthalmoscopic examination of the ocular fundi revealed moderate tortuosity of the retinal vessels, and slight dark pigmentation along the larger vessels. Lips and mucous membranes were moist, of fair color, with fine leukoplakia throughout the buccal mucous membranes. The gums showed some areas of sponginess. The tongue was moderately coated, lingual papillae were atrophic at the tip and along the lateral borders, and there was a slight coarse tremor. There was follicular hypertrophy and erythema of the pharynx. The thyroid was somewhat full, particularly on the right. A few small cervical glands were felt. The heart was moderately enlarged, the sounds were of good quality, the rhythm regular. Blood pressure was 118 systolic, 66 diastolic. There were a few fine crepitations at the base of the right lung. The abdomen was rounded and soft, and there was marked voluntary spasm with hyperesthesia. The liver was palpable two finger breadths below the costal margin. Pelvic examination revealed areas of glistening and erythema of the vaginal mucosa. There was a slight erosion of the cervix. Rectal examination was essentially negative except for small internal nonthrombotic hemorrhoids. The skin was dry and thickened. The skin of the face was mottled, with rare pustules and acne scars over the forehead, chin, and malar regions. Numerous tiny brown pigmented nevi were scattered over the body and the extremities. There were hypertrophic changes in the larger joints, particularly the knees, left shoulder, wrists and ankles, and early Heberden's nodes of the fingers and toes. Suggestive slight bilateral wrist and ankle drop was noted. The hands and feet were extremely cold, with pronounced mottling of the skin of the extremities. Dorsalis pedis and posterior tibial vessels were barely palpable. The toenails were somewhat thickened and ridged, and there was considerable ridging, depressions, and malformations of the fingernails. There was coarse tremor of the extended fingers. Reflexes were hyperactive, but none were pathological.

Laboratory data were at generally low normal levels. Basal metabolic rate was plus 12 per cent.

A high calorie, high vitamin diet was prescribed. Oral substitution therapy consisted of α -estradiol, a whole liver capsule, thyroid extract, vitamins A, C, D, with minerals, and a hydrolyzed protein powder. Parenteral therapy consisted of the anterior pituitary like factor, α -estradiol benzoate, liver extract, thiamine chloride, the whole vitamin B complex with ascorbic acid, pyridoxine hydrochloride, corpus luteum hormone, and deproteinized pancreatic extract. She was advised to continue to remain away from her work.

After one month of therapy the patient's general condition showed considerable improvement, with subsidence of many of her original complaints. She was less tense and irritable, and had not noticed any periods of extreme exhaustion. She was entirely free from abdominal pain and discomfort. At physical examination her hair was

more moist, of better luster, and the scalp was cleaner. Lips and mucous membranes were moist, and of good color; leukoplakia were diminished; the gums were firmer. Lingual papillae were much more pronounced, and there was no tremor of the tongue. The thyroid was smaller. Heart measurements were essentially normal. Blood pressure was 112 systolic, 68 diastolic. Lungs were essentially negative. The abdomen was less distended, but voluntary spasm and hyperesthesia persisted. The liver edge was barely palpable. Vaginal mucosa was more normal, and the erosion of the cervix was well healed. The skin was much more moist and of better color and tone. There were no new pustules, and many of the old ones were healed. The joints were more freely movable, and there was less creptus. Extremities were warmer, dorsalis pedis and posterior tibial vessels were more forceful on palpation. The nails were firmer and somewhat less ridged. There was no tremor of the extended fingers. Reflexes were less active.

Laboratory data were at good normal levels. Basal metabolic rate was plus 9 per cent.

For ten months the patient continued on the regime of oral and parenteral substitution therapy as previously described. During this period check-up examinations at regular intervals revealed definite improvement in physical and laboratory findings, and a pronounced improvement was observed in her general appearance, as well as in muscular power, emotional status and mental attitude. There had been no recurrence of abdominal pain. At the end of this time the question of permitting the patient to return to work was raised. Although clinically she appeared to be in good nutritional and endocrine balance, it was thought advisable at this time to make a complete laboratory study of her endocrine status.

The results of the tests as reported were as follows. Examination of the urine and blood, including blood serology, showed no abnormalities. Basal metabolic rate was plus 10 per cent. Blood follicle stimulating hormone (FSH) was normal. Blood cholesterol was 176 mg. per 100 cc. Fasting blood sugar was 92 mg. per 100 cc. of blood. Nonprotein nitrogen was 28 mg. per 100 cc. of blood. Total proteins were 6.2 mg. per 100 cc. of blood.

In view of the fact that all tests were essentially within normal limits the patient was allowed to return to work. Oral medications were continued, but parenteral therapy was stopped.

COMMENT

This case presents a problem in multiple vitamin and hormone deficiencies due chiefly to gastro-intestinal upset. The original hormone dyscrasia had followed typhoid fever and esophagitis at the premenarche period, and had been further complicated by a long period of faulty food intake attendant upon the esophagitis. Severe emotional and mental strain throughout puberty and during the following twenty years aggravated the vitamin and hormone deficiencies already present. The condition was further upset by occupational exposure to silver poisoning. The effect of all these etiological factors upon the gastro-intestinal tract was manifested by anorexia, constipation, abdominal pain, and distress. Although chemically there was no proof of silver poisoning, its possibility must be considered. The muscular weakness, joint pain, abdominal pain, suggestive wrist and ankle drop, and visual changes were all consistent symptoms. By first removing the patient from contact with silver, and then following this up with proper diet and complete

substitution therapy, a physiological balance was at length established. As we have seen, the gastro-intestinal symptoms subsided, as well as the general and neurological complaints.

The foregoing cases provide examples of common gastro-intestinal disease: the first case, cholecystitis and duodenal ulcer; the second, colitis; and the third, subacute argyria. In each case nutritional deficiencies resulted from the gastro-intestinal disease, and all three cases demonstrate the co-existence of vitamin deficiencies and endocrine dyscrasia as reported in previous publications (1, 3).

REDUCED DIETARY INTAKE

Case 1. A male, aged 33, complained chiefly of marked fatigue and lumbosacral backache of two years' duration, and presented an obvious history of reduced dietary intake. He had lived in Spain for four years during the recent Spanish Civil War, elsewhere on the continent for several months after the outbreak of World War II, and in London during the period of the Blitz. Food intake, for five years, because of food shortages, had been far below minimum dietary requirements. His general health had previously been good, but while in London he began to develop such symptoms as fatigue, palpitation, vertigo, increased nervous tension, headache, constipation, and back pain, and his hair had begun to get gray and thin. He lost 20 pounds.

Physical examination revealed a thin, well developed, fairly well nourished male, whose basal weight was 138 1/2 pounds, and height 68 inches. The hair was dry and lustreless, with beginning achromotrichia. The scalp was dry and scaling. There was two plus edema of the upper and lower eyelids. The pupils were slightly irregular, and reacted sluggishly to light and distance. The lips were cyanotic. Numerous fine leukoplakia were scattered over the buccal mucous membranes. A bluish line was noted on the upper and lower gums, which showed some areas of sponginess and recession. The tongue was slightly coated, and lingual papillae were atrophic along the borders and at the tip. The tonsils were hypertrophied, cryptic, and infected, and there was follicular hypertrophy of the pharynx. A few small cervical adenopathies could be palpated. The chest was symmetrical, barrel shaped, with a slight rachitic depression of the manubrium sternum. The heart was moderately enlarged, with sounds of fair quality, and some accentuation of the first mitral sound. Blood pressure under basal conditions was 85 systolic, 34 diastolic. The lungs were essentially negative except for a few fine crepitant rales after cough at the left base in the posterior axillary line. The abdomen was essentially negative. At rectal examination the prostate was large and boggy. The skin was somewhat dry and thickened, with numerous pigmented nevi on the body, face, and extremities. There was marked genu valgus. Extremities were cold, the fingernails were ridged and somewhat thickened. Pulsations of the dorsalis pedis and posterior tibial vessels were feebly palpable. Reflexes were somewhat diminished except for the ankle jerks which were increased.

Laboratory data were at low normal levels. Hinton blood test was negative. Basal metabolic rate was plus 7 per cent.

A well balanced diet was prescribed, of high vitamin and caloric content, and a regime of complete substitution therapy, both oral and parenteral, was instituted. Small amounts of thyroid, an elixir of the whole vitamin B complex, diethylstilbestrol, and capsules containing vitamins A, D, C, with minerals were given orally. Parenteral therapy consisted of the whole vitamin B complex with liver, thiamine chloride, liver extract, a-estradiol ben-

zoate, testosterone propionate, and the anterior pituitary like factor. Prostatic massages were given once per week. A month later tonsillectomy was performed.

This patient responded well to therapy, and following the tonsillectomy his improvement was accelerated. During the next two months he noticed gradual subsidence of all his subjective complaints, was much more energetic, less tense and nervous, was relatively free from backache, and gained four pounds. At his check-up examination three months after the beginning of treatment physical findings and laboratory data coincided with this improvement.

Physical examination at this time revealed the following. The weight was 142 1/2 pounds. The hair was moist and of good luster, the scalp was clean. No further progression of the achromotrichia was evident. There was no edema of the eyelids. The pupils reacted normally to light and distance. The lips and mucous membranes were of good color, moist, and only tiny residual leukoplakia remained. The gums were firmer, the bismuth line remaining. Lingual papillae were much more pronounced. The throat was essentially normal. Only a few small cervical adenopathies were palpated. The heart measurements were within normal range. The sounds were of good quality, and there was less accentuation of the first mitral sound. Blood pressure under basal conditions was 120 systolic, 70 diastolic. The lungs and abdomen were essentially negative. At rectal examination the prostate was smaller, with only slight boggiess in the left lobe. The skin was more moist and of much better tone. Many of the pigmented nevi were lighter in color. The extremities were warmer, dorsalis pedis and posterior tibial vessels were more forceful, and the nails were less ridged. Reflexes were normal.

Laboratory data were at optimal levels. Basal metabolic rate was minus 2 per cent.

COMMENT

This case serves as a clear cut example of nutritional disorders in which reduced dietary intake was chiefly responsible for the disruption of the synergistic activity of vitamins and hormones. The presence of infective foci in the tonsils and prostate complicated the picture. Correction of the resultant vitamin deficiencies and hormone dyscrasia could best be accomplished by eradication of the infective foci, and restoration of normal physiological balance through adequate diet and complete replacement therapy. Results in this case were prompt and gratifying. When last seen this patient had been maintained for two years at good levels on a minimum regime of oral medications, and had shown no tendency to recurrence of symptoms.

Case 2. This patient was a 40 year old, unmarried female, mentally retarded, with an intelligence quotient of a ten year old child. Her chief complaint was a scaly rash on both thighs of several months' duration. She complained also of mild abdominal pain and epigastric distress, severe anorexia, urinary frequency and urgency, nocturia, palpitation, swelling of the ankles, of approximately ten years' duration, all of which had become particularly marked during the year prior to consultation. Careful history showed this patient's food intake, over a period of several years, to have been very deficient in all essentials. Extraction of the teeth had been urgently advised by her dentist two years ago, but the patient had refused to have this done. For ten years her weight had remained at constantly low levels, averaging about 90 pounds. She had never had a menstrual period.

Physical examination revealed a thin, poorly developed, and poorly nourished female, whose weight was 92 1/2 pounds. The hair was dry and of poor quality. Conjunctivae were pale, the sclerae slightly injected. Ophthalmoscopic examination of the ocular fundi revealed moderate arteriovenous nicking and calibre changes of the retinal vessels. Lips and mucous membranes were moist, of good color, with extensive areas of leukoplakia on the buccal mucous membranes. The teeth were in very bad condition, some were missing, and there were many caries and roots. The gums were spongy, and showed evidence of infection especially about the carious dead teeth. The tongue was of the geographic type and presented a fine tremor. Lingual papillae were markedly atrophic. The breasts were of the male type. Heart sounds were of good quality, the rhythm regular. Blood pressure was 102 systolic, 54 diastolic. The abdomen was rounded, soft, and there was some voluntary spasm. Rectal examination revealed an infantile type of uterus. The skin was dry and roughened, and there was a scaly macular rash on both thighs. Hypertrophic changes were evident in the larger joints, with pronounced Heberden's nodes of the fingers. Extremities were cold. The nails were slightly cyanotic, thickened and ridged. Dorsalis pedis and posterior tibial vessels were feebly palpable. Reflexes were hyperactive.

Laboratory data were at low or subnormal levels. Basal metabolic rate was plus 20 per cent.

A full, well balanced diet, of high vitamin and caloric content was prescribed. Extraction of the carious and dead teeth was strongly recommended. Because the patient was somewhat uncooperative no parenteral substitution therapy was given at this time, and only a mild regime of oral medications was prescribed, consisting of thyroid extract, the whole vitamin B complex, and α -estradiol. An antipruritic ointment was given for the skin rash.

This patient was a somewhat difficult one to treat. She refused to have the carious teeth extracted or taken care of in any way. During the first few weeks of therapy she followed her regime of medications and adhered to her diet fairly well, but later became uncooperative in this regard as well. Despite this, however, her general condition showed considerable improvement, the skin rash cleared completely, and she showed a slight gain in weight. Subjective complaints subsided somewhat, although the patient was loath to admit any improvement. However, physical and laboratory findings at periodic check-up examinations repeatedly gave evidence of this improvement.

At examination ten months after the start of therapy her weight was 108 pounds. The hair was more moist and of better quality. Conjunctivae were of good color; the sclerae slightly injected. Lips and mucous membranes were moist, and only residual areas of leukoplakia remained. The gums were somewhat improved, the caries and roots remaining. The tongue was slightly coated. Lingual papillae were more pronounced, and there was no tremor. Blood pressure was 104 systolic, 62 diastolic. Abdomen was essentially negative. The skin was more moist and of much better tone, and the rash on the thighs had cleared. The joints were more freely movable. Extremities were warmer, and the peripheral vessel pulsations were more forceful. The nails were of normal color, firmer, and less ridged. Reflexes were more normal.

Laboratory data were all at good normal levels. Basal metabolic rate was plus 2 per cent.

At about the end of the first year of therapy the patient was given a short course of parenteral therapy. After eight injections of estrone in dosage ranging from 10,000 units to 40,000 units, and 250 units to 500 units of the anterior pituitary like hormone, the patient had her first menstrual period. For five months the cycle recurred at almost regular intervals, but the sixth month there was only staining, and thereafter ceased completely. During the

five months of regular menstruation there was a slight increase in growth and development of the uterus and breasts, returning to their original condition with termination of the periods.

For seven years this patient has been maintained at relatively normal levels. She has refused to permit extraction of the carious teeth, but has been fairly cooperative in adhering to her diet and in following her regime of oral substitution therapy. From time to time there has been a mild return of symptoms which have responded well to short courses of crude liver injections. Her weight has ranged between 105-110 pounds.

COMMENT

In this patient with congenital ovarian deficiency we have an illustration of reduced dietary intake as a consequence of carious teeth and gingivitis, which produced severe nutritional deficiencies. Failure of the patient to cooperate fully prevented achievement of optimal therapeutic results. But a full diet, mild oral substitution therapy with vitamins and hormones, supplemented at intervals by parenteral liver, was effective in restoring adequate physiological balance and in giving this patient relief.

In passing, it is of interest to observe that despite primary amenorrhea throughout the entire reproductive years, regular menstruation was established for a five month period, even though so late in life, and at a time when the climacteric period might be expected. To be noted also is the fact that her best nutritional status and weight level was obtained at the same time. It must therefore be concluded that restoration of normal endocrine activity, even though infection has been only partially cleared, can bring about an improved synergy between vitamins and hormones, which results in a more nearly normal physiological balance.

Case 3. A 35 year old, unmarried female, complained of irregular and painful menstruation of nine years' duration, and acne of the face which appeared six months ago. Catamenia had always been normal until nine years ago, when, following an appendectomy the periods became irregular, and were accompanied by pre-menstrual tension and breast fullness, backache, severe dysmenorrhea, and excessive flow. Another operation four years ago, including dilatation and curettage, myomectomy, and right oophorectomy, afforded the patient only temporary relief. The following year radium implantation was performed for the excessive bleeding, after which menstruation was delayed, with one period of amenorrhea of four months' duration. Since then periods had come in cycles of six to eight weeks, menstrual flow became more normal, but premenstrual symptoms and dysmenorrhea remained the same. For the past two years vaginal discharge, accompanied by pruritus, had been constant and severe, particularly so just before the menstrual period. Complaints such as extreme fatigue, headaches, constipation, flushes, palpitation, and emotional imbalance became more pronounced, and she observed increasing dryness of the hair and skin. For the past ten years, following an intestinal infection, there had been marked decrease in appetite and gradual loss of weight. She lost 15 pounds in the past year.

Physical examination revealed a well developed, fairly well nourished female, whose height was 64 inches, and weight under basal conditions 113 pounds. Her hair was lusterless and dry. The scalp was dry and scaly. The upper and lower eyelids were markedly edematous and

reddened. Sclerae were slightly injected, and there was a mild chronic conjunctivitis. Ocular pressure was slightly increased. Lips and mucous membranes were moist and of fair color. There was considerable general thickening of the buccal mucous membranes, and a few areas of greater thickness resembling keloid. The gums showed some areas of recession. Lingual papillae were atrophic, and there was marked denudation at the tip and peripheral borders. The thyroid was full, particularly on the right. The heart was somewhat enlarged. Sounds were of good quality, regular, slow. The first mitral sound was accentuated, and there was a slight reduplication of all sounds. Blood pressure was 105 systolic, 64 diastolic. The breasts were small, and there was slight thickening through Cooper's ducts. The lungs and abdomen were essentially negative. Pelvic examination revealed a slight cystocele, marked redness and edema of the vaginal mucosa, and a small erosion on the cervix. The uterus was slightly enlarged. Rectal examination showed a tight sphincter, but otherwise was essentially negative. The skin was dry. Numerous tiny pigmented nevi were distributed over the body. Acneiform lesions were scattered over the whole face, but were concentrated particularly about the chin and mouth. There was slight thickening through the interphalangeal joints of the fingers and toes. Extremities were cold. The nails were somewhat thickened and brittle. There was slight coarse tremor of the extended fingers. Reflexes were hyperactive.

Laboratory data were at generally low normal levels. Basal metabolic rate was minus 9 per cent. Hemoglobin was 80 per cent, red blood cell count was 3,930,000, white blood cell count 7100.

A full diet was prescribed, restricted only with due regard for the acne. A complete regime of oral and parenteral substitution therapy with vitamins and hormones was initiated. Oral medication consisted of thyroid extract, an elixir of the whole vitamin B complex, calcium, α -estradiol, para-aminobenzoic acid, and riboflavin. Anterior pituitary like hormone, corpus luteum hormone, α -estradiol benzoate, testosterone propionate, thiamine chloride and liver extract were given parenterally. Local therapy for the acne consisted of two special creams* containing a synthetic hormone, alone in one cream, and in combination with vitamin A in the other. A report of these creams will be published later.

Response to this therapeutic regime was excellent. There was prompt improvement in the patient's general condition, and gradual subsidence of most of her subjective complaints. Within four months acneiform lesions were almost entirely absent. Menstrual periods were well regulated as to interval and flow, with complete absence of premenstrual symptoms or dysmenorrhea. She felt much more energetic, and emotionally was more stable. Physical and laboratory findings at frequent check-up examinations corresponded with this improvement.

Physical examination six months after the beginning of therapy revealed the following. The weight was 117 pounds. The hair was more moist and of better luster. Edema of the eyelids had completely subsided, and only slight redness remained. Conjunctivae and sclerae were clear. Lips and mucous membranes were of much better color, and the areas of thickened buccal membranes were less pronounced. The gums were firmer. Atrophic areas on the tongue were well filled in, and lingual papillae were pronounced. The thyroid was smaller. Heart measurements were more normal. Accentuation of the first mitral sound was diminished. Blood pressure was 112 systolic, 72 diastolic. At pelvic examination the vaginal mucosa was more normal, and revealed none of the redness and edema ap-

* Material supplied through the courtesy of Mr. Henry G. Esdall, of the Anabul Laboratories, Inc., 281 Franklin Street, Boston Massachusetts. Trade name "Diestil Cream" and "Diestil A Cream."

parent at the original examination. The erosion of the cervix was healed. Slight thickening persisted through the interphalangeal joints of the fingers and toes. The skin was more moist and of much better tone. Aeneform lesions and superficial scars were completely cleared. Pigmented nevi were lighter in color. The extremities were warmer, the nails were firmer, and less thickened, and there was no tremor of the extended fingers. Reflexes were normal.

Laboratory data were at good normal levels. Basal metabolic rate was plus 3 per cent. Hemoglobin was 98 per cent, red blood cell count 5,140,000, white blood cell count 8,000.

At the end of the first two months of therapy, under the original regime as described, the patient had responded so well that an attempt was made to reduce parenteral therapy. The result was definite and rapid regression in both the physical and laboratory findings. In order to maintain normal levels it was necessary to keep this patient on a schedule of parenteral therapy at bi-weekly intervals for three years. At the end of this period the whole liver capsule and the hydrolyzed protein powder became available, and were added to the oral medications. Parenteral therapy was continued twice a week, and other oral medications remained the same. One month after the addition of these two new factors to the regime, parenteral therapy was given but once a week, with no ill effects. Two months later it was possible to omit parenteral therapy entirely for two to three months. Then a booster course of injections was necessary for four to five weeks, following which they could again be suspended.

The addition of the whole liver factor with liver lipoids, and further fortification with the essential amino acids, was without question a valuable supplement to the therapeutics in this case. The patient's general well being, the continued improved condition of her skin, the regularity of the menstrual cycle with absence of dysmenorrhea, and the added gain in weight to a new high of 125 pounds, were all indications of good nutrition, and the establishment of almost complete physiological balance.

COMMENT

The salient feature in this case is the inadequate food intake over a period of ten years, the result of anorexia following an acute infection. This infection initiated a commonly observed train of events which led to a marked nutritional imbalance. Two surgical operations only served to upset the menstrual cycle, and to add hormonal disturbance to the food and vitamin deficiency. An attempt to help the menstrual dysfunction by the use of radium produced partial castration and further complicated the situation. So, throughout the entire decade the patient not only remained on a low food intake, but her organism was unable to completely utilize ingested food, to absorb or synthesize sufficient vitamins or to secrete an adequate supply of hormones. The approach of normal menopause upset the nutritional and endocrine pictures still further. By substitution therapy, plus the removal of foci of infection in the liver, cervix and skin, physiological balance was obtained. The fact that continuous parenteral therapy was essential over a three year period was a good indication that an essential element in balance had been missing, possibly an enzymic action or a catalytic agent. It would appear that introduction of the whole liver factor with liver lipoids, and all the known essential amino acids in high con-

centration, provided this missing element in balance.

These last three cases illustrate the effect of reduced dietary intake in disturbance of the synergistic activity of vitamins and hormones. Case 1 is a clear cut example of inadequate diet due to war time food shortages. In the second case carious teeth, and in the third anorexia as a result of the chain of circumstances as described, were chiefly responsible for the inadequate diet. In all three patients severe nutritional disorders and endocrine dyscrasia resulted. When hormonal balance had been restored by means of complete substitution therapy with vitamins and hormones, and any existing infection had been eradicated, then the adequate diet prescribed could be properly metabolized and utilized. Only then could proper physiological balance and good nutritional status be achieved.

The favorable response obtained when the whole liver capsule and hydrolyzed protein powder were added to the therapeutic regime would seem to indicate, as mentioned before, that an essential element in balance, heretofore missing, had been supplied. Although the whole liver capsule contains some of the amino acids, which may account for the earlier observations reported (3), it seems apparent now, on the basis of more recent experience, that the hydrolyzed protein powder contains the active agent, serving probably as a catalyzer or enzyme for complete utilization of the elementary food factors. This apparent action of the hydrolyzed protein powder suggests that possibly our normal food intake should be broken down even more into its constituent elements, and then administered as a dietary supplement in the form of a hydrolyzed protein. It could be fortified further by the addition of the whole liver concentrate which contains the lipoids, as well as the additional amino acids and vitamins. Such a combination should enhance vitamin and amino acid utilization, and, conversely, improve hepatic function. Improved liver function would in turn enhance the utilization of hormones and vitamins, and improve the metabolism of food elements — carbohydrates, proteins, and fats. This improved physiological function would necessarily lead to a physiological balance and a better nutritional status.

In special reference to the hydrolyzed protein used in these cases it might be well to point out that it is a 94 per cent hydrolyzed protein obtained from both meat and milk protein factors. It must not be confused with the many other available hydrolyzed proteins which are purely casein derivatives from milk. Several of these milk derived hydrolyzed proteins had been given adequate clinical trial before the present product became available, but none gave as good results, even though, biochemically speaking, the source should not matter when the protein is in hydrolyzed form. Since reporting this original series we are convinced by trial in a larger series of cases, that the addition of this hydrolyzed protein to the oral medication has enabled patients who previously had required continuous parenteral therapy with hormones and vitamins to go for relatively long periods without any parenteral therapy other than short booster courses at various

intervals. A detailed report on this hydrolyzed protein powder, based on a more extensive series of cases, will be submitted later.

CONCLUSIONS

1. Gastro-intestinal disease and reduced dietary intake constituted the chief predisposing causes in 67 per cent of a series of 200 cases of nutritional disorders.
2. Gastro-intestinal disease may be the primary result of specific pathology in the gastro-intestinal tract, or secondary to systemic disease which can be controlled indirectly by vitamin and endocrine therapy.

3. A careful, detailed history, with particular reference to food habits and attention to the condition of the mouth, may uncover unsuspected reasons for reduced dietary intake.
4. Consideration of the patient as a whole, with particular attention to the presence of infection and to the vitamin-hormone balance, usually provides the key to proper substitution therapy, which should supplement a well balanced diet.
5. The importance of two new therapeutic agents is discussed: a capsule containing the whole liver factor with lipoids of liver, and a highly concentrated hydrolyzed protein powder.

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Nutrition Notes

Army Ration Trials and Surveys, 1941-1946

Robert E. Johnson, M.D. and Robert M. Kark, M.R.C.P. (London) of the Harvard Fatigue Laboratory, Boston, Massachusetts, formerly the Director of the W. D. Medical Nutrition Laboratory, have presented in great detail a report, "Feeding Problems in Man as Related to Environment," which is issued by the Quartermaster's Food and Container Institute for the Armed Forces, with the usual cautious *proviso* that the opinions or conclusions contained in the report are those of the authors and do not necessarily reflect the views or indorsement of the War Department. The report deals with nutrition experiments on a large scale in the U. S. A. and Canada, especially with respect to the food needs of active soldiers, and runs to nearly 100 pages, and issued by the Office of the Quartermaster General, Chicago 9, Illinois. Some of these experiments were conducted in the U. S. A., some in England, some in Canada and Alaska and even India. The well publicized operation "Musk Ox" is included. A wide variety of climates,

altitude and terrain were employed. Temperatures varied between the extremes of -45° to 120° F and altitudes from sea-level to 9000 feet. Various rations including some used by the Canadian and British Armed Forces as well as the more familiar rations employed by the U. S. A. forces formed the basis of the experiments. During the war a large volume of data were obtained on the feeding of U. S. and Canadian troops subjected to differing environmental conditions. Observations were made at home and abroad by survey teams, by civilian and army laboratories and by test agencies that had conducted ration trials. The present report deals chiefly with field tests between 1941 and 1946 in Arctic, sub-arctic, temperate, mountain, desert, tropical and sub-tropical areas, and constitutes a *definitely valuable contribution* to the understanding of the problems involved in feeding men under all environmental conditions. The writing of the report was completed under a contract between the Quartermaster Corps, U. S. Army and Harvard University.

There are countless important points which cannot

be touched upon in commenting on this important report, because of the heterogeneous nature of the methods employed, but it is true that two major conclusions emerge, and each is not only simple but impressive. *First*, dehydration produces deterioration in troops through exhaustion, and it is essential to supply active young men with enough water to drink to keep thirst quenched *at all times* and under all conditions. Men cannot actually be "trained to do without water." *Second*, operational inefficiency was caused strikingly by *caloric deficiency* in soldiers and not at all, within the periods of the experiment, by the partial exclusion of the vitamin B complex. This reflects the home-spun wisdom of some farmers who feel that what "*a fellow needs is something to eat*." In their application to civilian life the chief conclusions of this able report may suggest chiefly this: that in our concern with vitamins, we ought not, as physicians, to forget that the caloric requirements of individuals, both sick and well, need definite consideration especially in cases where we are striving to improve the efficiency of the human machine.

Fatty Liver Disease in Infants in the British West Indies

Professor B. S. Platt, Director of the Medical Research Council's "Human Nutritional Research Unit" found a peculiar and dangerous disease of infants in the British West Indies which he attributed to their being fed on a *diet low in protein and high in carbohydrate*. In 1945, Dr. J. C. Waterlow went to Trinidad, British Guiana and Jamaica and confirmed and extended the previous observations. Waterlow's valuable report is issued by the Medical Research Council in a book of approximately 100 pages and may be obtained by sending two shillings to H. M. Stationery Office, 429, Oxford Street, London, W. 1. or from the British Library of Information, 50 Rockefeller Plaza, New York, N. Y.

This fatty liver disease in infants has been clearly differentiated from infantile marasmus and kindred conditions. The most important feature observed was fatty infiltration of the liver, which appeared to determine the clinical course and severity and was used as a diagnostic criterion. This was accompanied by edema and muscular wasting without total loss of subcutaneous fat. In the West Indies, mucosal and subcutaneous signs of vitamin-B-complex deficiency, which in other parts of the world may dominate the clinical picture, were slight or non-existent. There was no response to treatment with pure lipotropic substances, but considerable improvement occurred on a high intake of milk. Evidence was obtained that this disease may be the precursor of portal cirrhosis developing in childhood — a condition that is not uncommon in the tropics. Dr. Waterlow's work, as embodied in this report, is important because it links the striking findings of animal experimentation in this field with a serious nutritional disease in the human subject, and with this ground established an intensified study of nutritional disorders of the liver may be expected. It is important also because it draws attention to a particular nutritional defect which may well play

a considerable part in producing the very high infant mortality rates pertaining in many colonial territories.

The syndrome observed in the West Indies clearly belongs to a group of related conditions, described in recent years in many tropical countries. Trowell, working in Uganda, described a disease there known as the "Kwashiorkor Syndrome." It occurred shortly after weaning and was characterized by edema, "crazy-pavement" skin, diarrhea, cheilosis, stomatitis, generalized pallor of the skin and pale, straight scanty hair. Microcytic and macrocytic anemia and steatorrhea were variable factors and the mortality was between 40 and 60 per cent. The fatty infiltration found at autopsy was regarded as a terminal phenomenon of little significance. Gillman and Gillman were the first to emphasize the fundamental importance of the hepatic lesion, and their discovery of the curative value of *dessicated stomach* was a notable contribution to our knowledge of this disease. Trowell maintained for a long time that the important components of the disease were pellagra and nutritional edema but later introduced the more general term "malignant malnutrition." Cases with features suggesting the same disease have been reported from Haitai, Kenya, Belgian Congo, Costa Rica, Guatemala and China. Most authors believe that all cases of this general type are due to dietary deficiency, probably multiple in character.

At post-mortem the liver is yellow and friable, the cut surface greasy, bulging and sometimes bile-stained. Microscopically, any cell is distended by a large fat globule.

The only hepatic function test that was of any value in these cases was the bromsulphalein clearance. Liver biopsies were accomplished with no ill effects by means of a needle. In no case was albumin found in the urine. Glossitis was common but achylia did not exist. Severe liver damage may be present without dermatosis, glossitis, edema or *any superficial signs*, in which case diagnosis rests on finding hepatic enlargement. Edema is an important warning sign. These infants are sometimes referred to as "sugar babies" because of the high sugar content in their habitual diets.

Methionine, choline and inositol had no apparent beneficial effects. Milk was the sheet-anchor of treatment. Mild cases recurred when milk was used but once the disease became deeply established the mortality was high. Some evidence suggests that vitamins aggravate the disease. Dried stomach and liver extract injections showed a good response in the cases of Gillman and Gillman, and these agents are superior to milk. Low protein intake appears to be one of the chief etiological factors and it is possible that some protein element common to milk, dried stomach and liver extract is responsible for improvement noted.

This valuable investigation under the Privy Council Seal and the Medical Research Council undoubtedly will be further prosecuted, and may, incidentally, contribute greatly to our knowledge of the role of protein feeding on various types of liver disease.

Abstracts on Nutrition

HOVANIC, K. J.: *Blood diastase studies in acute epidemic parotitis*, (Arch. Pediat., Jan. 1948, V. 65, No. 1, 1-5).

In 58 of 80 cases of acute epidemic parotitis the plasma level of starch-splitting diastase was higher than the normal range, and the author believes that such determinations are of value as a diagnostic measure.

KINSEY, V. E.: *Nutrition and ophthalmology*. (Nutr. Rev., March 1948, V. 6, No. 3, 65-66).

In the opinion of some 27 practicing ophthalmologists in Boston, who collectively examine about 30,000 cases annually, nutritional deficiency played a definite role in eye disease in only about 0.1 to 0.2 per cent of cases. In other parts of the world it is true that inadequate nutrition may be a factor of paramount importance in ocular disease. Experimental work has shown the need of riboflavine, tryptophane, lysine and methionine to maintain normal corneal physiology. Vitamin A in adequate supply is essential for the transmission of light stimulus into nerve impulses. The transmission of nerve impulses appears to depend upon adequate supplies of thiamine as indicated by reports of improvement in conduction defects and retrobulbar neuritis with beriberi following thiamine therapy. The cerebral process by which impulses set up by the retina are integrated into visual patterns do not appear to be related to any known nutritional deficiencies.

SUNDARESON, A. E.: *The relation between infantile cirrhosis of the liver and a diet of polished rice*. (J. Indian Med. Assoc., V. XVI, No. 10, July, 1947, 335-340).

It would appear that infantile cirrhosis of the liver in India is most prevalent in those areas where rice forms a staple article of diet — Bengal, Madras Provinces, in the deltas of the great rivers and the long strip of land fringing the coast. In Java, where the population lives almost exclusively on rice, mortality from cirrhosis is 10 times that seen in an European population of the same age and sex in Holland. The disease occurs almost exclusively among the rich upper and middle class families who prefer the highly-milled, white rice. Experiments were carried out on suckling rats and it was found that extensive necrosis and hydroptic degeneration occurred in the livers of sucklings whose mother's diets, in addition to the basic rice ration, were deprived of either yeast or meat in the diet. The greater the amounts of yeast, meat or casein in the diets of the mothers, the less the degenerative changes observed in the livers of the sucklings. Casein had the least protective action.

GILLMAN, J. AND GILLMAN, T.: *Malnutri-*

trition and pellagra in South Africa. (Nutr. Rev., Dec. 1947, V. 5, No. 12).

Malnutrition is spectacular both among the European and native population in South Africa. In the Transkei, less than one per cent of school children have three meals per day. Even in towns, qualitative and quantitative deficiency exists in animal protein, fats, calories, vitamins and salts, with maize as the staple of the diet. All dietary surveys of the past decade reveal the prevalence of gross malnutrition, and an extremely high infant mortality rate in certain sections — of 1426 children born alive, 36.4 per cent died before the age of two, and 46.1 per cent before the age of 16 years. The onset of puberty in girls is significantly delayed. One-third of European children are malnourished. Among 7,000 African (negro) children, the incidence of malnutrition was 71 per cent. Pellagra has now become endemic in Johannesburg. In four years, over 4,000 cases have been recognized.

In infants the syndrome is characterized by edema, dermatosis, graying of the hair, alopecia, steatorrhea and intensely fatty liver with a mortality rate some years as high as 60 per cent. Fifty per cent of infants under two years, dying from all causes, have rickets. In adult pellagrins, the incidence of liver disease is high. 12.5 per cent showing cirrhosis and 30 per cent pre-cirrhosis. In Africans dying from accidents, but presumably healthy, the incidence of liver disease was 70 per cent with 9.4 per cent suffering from cirrhosis. Primary carcinoma of the liver accounts for 90 per cent of all carcinomas in young male subjects in the Gold Mines. The Gillmans and others have shown that feeding rats with maize meal and fermented milk produces liver damage including cirrhosis and cystic fibrosis of the pancreas. The malnutrition possibly is significant in determining the low incidence of peptic ulcer, hyperthyroidism, prostatism, urinary and biliary calculi and diabetes, and facilitating the premature senescence, hypertension and arteriosclerosis in Africans.

CLEMENTS, F. W.: *Clinical manifestations of deficiency diseases in infants and children: a study in chronic malnutrition*. (Med. Jour. Australia, August 23, 1947, V. II, No. 8, 225-231).

Chronic malnutrition in children at school age is shown by a lack of subcutaneous fat, poor muscle tone, poor posture, and repeated low grade infections, as well as loss of weight. The latter, by itself, may not indicate chronic malnutrition. Among the causes are acute illnesses, deficiency diseases and psychological feeding problems. Metabolism is a very dynamic activity, the two phases of which are influenced by specific enzymes. The author emphasizes the practical importance of low protein intake and deficiency

in vitamin C, thiamin and vitamin D. Young children need 40 to 45 grams of protein daily and in Australia, despite prevailing high standards of living, it is astonishing how many children fail to get this much. A formula for figuring the daily protein contents in the diet is presented.

THOMAS, E. M.: *Total and fractional blood lipids in diseases of childhood*. (Amer. J. Dis. Child., Nov. 1947, V. 74, No. 5, 563-575).

Bloor's colorimetric method was used and 50 children with various diseases were studied, using 24 normal children as controls. Seriously abnormal lipid levels were found in patients with nephrosis, hypothyroidism, glycogenosis and hepatic parenchymal disease. In nephrosis, a preponderance of cholesterol in the early stage was replaced by a decided excess of neutral fat during severe phases when the total lipid was highest. Of two children with cretinism, one showed a higher relative cholesterol level and a lower neutral fat level than the other. A moderate drop in total lipid levels occurred in one patient during the active phase of subacute catarrhal jaundice. High

and variable total lipid levels were found in a patient with glycogenosis. Uniform moderate increase of all the lipids occurred in patients with carotenemia.

SCHWARTZMAN, J., CRUSIUS, M. E. AND BEINE, D. P.: *Diabetes mellitus in infants under one year of age*. (Am. J. Dis. Child., Nov. 1947, V. 74, No. 5, 587-606).

A case of an eight month old girl with diabetes mellitus is reported and 57 cases of the disease in infants under one year are reviewed. Heredity, infectious and central nervous system disorders were the main etiological factors. There were three cases of hydrocephalous in the series. Early symptoms were weight loss, dry skin, irritability and crystalline deposits on the diapers. Gangrene, cataract, respiratory infections, acidosis and coma were the common complications. Post-mortem, atrophy of the pancreas and fatty degeneration of the liver were commonest findings. Treatment was based on a fairly normal diet, insulin and vitamins. When the onset of the disease occurs before the third month, the prognosis is the worst.

General Abstracts Of Current Literature

ABSTRACT EDITOR — M. H. F. FRIEDMAN

Jefferson Medical College

1025 Walnut Street

Philadelphia, Pennsylvania

MOUTH AND ESOPHAGUS

WHEELER, DIGBY: *Diverticula of the foregut*. (Radiology 49, 4, 476. October 1947).

The author describes diverticula of the different portions of the foregut and shows roentgenograms of his cases. With the exception of the diverticula at the pharyngeal-oesophageal junction, they are usually incidental findings. The oesophageal-pharyngeal diverticula produce definite symptoms, the others are practically asymptomatic. Diverticula of the lower oesophagus are important when instrumentation is contemplated. Because diverticula are so readily demonstrated by an X-ray examination, their significance, except for the oesophageal-pharyngeal type, has been greatly exaggerated.

FRANZ J. LUST

GILLMAN, J., GILBERT C., AND GILLMAN, T.: *The Bantu salivary glands in chronic malnutrition with a brief consideration of the parenchymal interstitial tissue relationship*. (S. African J. Med. Sci. Dec. 1947, V. 12, No. 3, 99-109).

The salivary glands, no less than the liver, the

pancreas and the kidney, are implicated in the disturbed metabolism in Africans (Bantu) induced by chronic malnutrition, showing such reactions as general atrophy, low-grade fibrosis, followed later by atrophy of the parenchyma, cystic fibrosis and cytosiderosis. An overgrowth of connective tissue can occur in the salivary glands without being necessarily preceded by injury to the parenchyma. Overgrowth of connective tissue is not necessarily related to parenchymal injury but may be due to the irritation of the reticulo-endothelial system by metabolites elaborated in the course of malnutrition or admitted via an altered intestinal mucosa. The same may apply to the liver.

JORSTAD, L. H.: *Diagnosis and treatment of carcinoma of the buccal mucosa*. (Miss. Valley Med. J., March 1948, V. 70, No. 2).

Over 95 percent of buccal mucosal cancer is squamous-celled carcinoma and the disease occurs predominantly in the male. Adequate removal or destruction with actual cautery is the most effective form of treatment for the primary lesion. Reconstruction procedures are usually delayed for a period of 12 months during which there must be no recurrence of cancer.

Resection of the regional lymph bearing tissue (neck) is indicated only in those cases where lymph nodes are enlarged and their enlargement is due to metastases.

BOURNE, W. A.: *Sclerodactylia with esophageal lesion*. (Proc. Roy. Soc. Med., Jan. 1948, V. XLI, No. 1, 43).

A patient developed increasing dysphagia apparently due to pharyngeal incoordination and died suddenly. The post mortem showed, in addition to the sclerodactylia, diffuse change affecting the intestinal tract, the pericardium and probably the heart muscle and pleura. The upper esophagus appeared normal but at the lower end there was increased opacity and thickness of the epithelium (leukoplakia) down to the cardia. There was a scar of a small healed ulcer in this region as well as a fairly marked hernia of the stomach through the esophageal hiatus.

STOMACH

ROACH, COMMANDER J. F. AND POPPEL, COMMANDER M. H.: *The roentgen demonstration of an aberrant pancreatic nodule in the stomach*. (Am. J. Roentgen and Rad. Ther. 56, 5, 586. November 1946).

Accessory or aberrant pancreas appear as rounded, flattened tumors varying in size up to four cm. in diameter. They may be single or multiple. They may occur anywhere in the stomach, small bowel, mesentery, or omentum. They have been found within duodenal or Meckel's diverticula. They may have independent excretory ducts sometimes opening on papillary elevations. They seldom contain islands of Langerhans, but if present they are usually deformed. Small myomas (adenomyomas) may develop around aberrant pancreatic nodules.

Roach and Poppel report three cases of aberrant pancreatic nodules, which they were able to demonstrate by roentgenological examination. They had the appearance of small, round tumors, best seen on the mucosal films. The authors show the microphotographs of the lesions.

Only three hundred cases of these benign tumors are on record.

FRANZ J. LUST

WALTERS, W., GRAY, H. K. AND PRIESTLY, J. T.: *Report on surgery of the stomach and duodenum for 1946*. (Proc. Staff Meet. Mayo Clinic, Jan. 21, 1948, V. 23, No. 2, 29-37).

Only 14 per cent of all patients with duodenal ulcer were operated upon, indicating a conservatism which may be carried too far. In duodenal ulcer, partial gastrectomy was done in 70 per cent of cases and gastro-enterostomy in practically all of the other 30 per cent operated upon. Mortality was about equal for both procedures and the total mortality was 1.6 per cent. Vagotomy is an operation not viewed with favor because of the troublesome sequela, and should be confined to patients with gastrojejunal ulcers after partial gastrectomy.

EUSTERMANN, G. B.: *Annual report on the stomach and duodenum for 1946: medical aspects*. (Proc. Staff Meet. Mayo Clinic, Jan. 21, 1948, V. 23, No. 2, 38-39).

Pre-operative pyloric obstruction increases the risk factor in surgery. The treatment of dehydration, electrolytic imbalance, anemia, hypoproteinemia and the use of selective anesthesia and antibiotics contribute to the good surgical statistics. Vagotomy is on the wane. Subtotal gastrectomy is the operation of choice, in spite of recurring ulcerations and the so-called "dumping" syndrome.

KOWALEWSKI, K.: *A study of gastric acidity in prisoners of war suffering from various gastro-intestinal troubles*. (Acta Gastro-Ent. Belgica, Nov.-Dec. 1947, V. X, 8-9, 503-513).

1890 prisoners of war suffering from various gastro-intestinal complaints were examined by fractional gastric analysis following testmeals. An important and progressive increase of cases showing achylia and hypo-acidity were noted during the years 1941-1944. This is thought to be attributable to prolonged low protein intake, abetted by multiple hypovitaminoses and the unusual psychological conditions.

PEARSON, C. C.: *Present status in gastroscopy*. (Bull. Mason Clinic, March 1948, V. 11, No. 1,).

The mortality from gastroscopy was found to be 0.004 per cent in a series of 22,351 operations done by sixty gastroscopists. Contraindications for the operation are esophageal disease, serious cardiac impairment, corrosive gastritis, peritonitis, etc. It is valuable in disputable cases where there is doubt as to whether treatment ought to be medical or surgical; in the presence of gastric lesions not detectable by X-ray; unexplained gastro-intestinal hemorrhage, and for substantiation of the diagnosis of chronic gastritis. Sometimes visualization of the interior of the stomach is necessary even when a cancer or ulcer is known to be present, especially to determine operability.

COMFORT, M. W., KELSEY, M. P. AND BERKSON, J.: *Gastric acidity before and after the development of carcinoma of the stomach*. (Proceed. Staff Meet. Mayo Clinic, Mar. 17, 1948, V. 23, No. 6, 135-142).

In order to cast light on the problem of what produces the lowered acidity so commonly found in the gastric juice of patients suffering from cancer of the stomach, 277 patients were selected in whom gastric analyses had been done and recorded two or more years prior to the diagnosis of carcinoma. It was found that the mean secretory activity had been subnormal at a mean interval of 11.2 years before the diagnosis of cancer was made. Acidity was subnormal as far back as the third decade of life of the individual involved. The authors favor the view that chronic atrophic gastritis is responsible for the lowered acidity by destruction of acid-secreting cells, before the development of the cancerous lesion.

The Treatment of Obesity *

By

MAX GOLDZIEHER, M.D.

NEW YORK, N. Y.

THE PREVAILING CONCEPT OF OBESITY is based on the assumption that a gain in weight represents always an excessive intake of food. It is true that investigation of the dietary habits of the obese patient often reveals excessive food intake though no adequate statistics are available to show how large a percentage of the obese population actually overeats and how many eat no more or even less than the average. Considering the prevailing dietary pattern of our population with its emphasis on carbohydrate and fat, we might wonder why most of the people are not obese. On the other hand, physicians who see a large number of obese patients, time and again are confronted with the claim that the patients subsist practically on a starvation diet and even that is hardly adequate to prevent a gain in weight.

These observations, however, are discounted and explained as the result of unadmitted eating, for according to the caloric school, it would constitute a violation of the laws of thermodynamics to consider even the possibility that a person could gain weight on food intake less than the calculated caloric requirements. This view assumes an unchanging efficiency of body metabolism, independent from the internal environment and from the effects of the manifold catalytic agents, hormones, etc. which are supposed to regulate the chemical reactions of the body. The caloric school is not much concerned with the facilities engaged in the limitation of the waste of energy, be it as actual heat or in any other form; nor do they like to enter the discussion of the variable energy requirements for tissue synthesis which can be satisfied with fewer calories than we are accustomed to think as necessary (Cannon 2), so that the remaining surplus may become available for storage in the form of fat. Actually the chemical processes which go on in the body are far more complex than for instance the assumed burning of carbohydrate to carbon dioxide; the intricacies of these processes are not suitable for the simplifications of the caloric school which had to give up already some of their former mainstays such as the D/N ratio or ketogenic/antiketogenic ratio as untenable figments of a mechanistic imagination.

According to the caloric theory of obesity, it is maintained that appropriate restriction of food intake reduces weight in accordance with prediction in every case. This is undeniably true for complete starvation which causes weight loss irrespective of the patient's constitution or metabolic status. Even 450-600 calories

as recommended by Evans and Strang (3) and other orthodox nutritionists, though not constituting actual starvation levels, do accomplish weight reduction in practically all cases, yet it is doubtful whether such a diet can be enforced for any length of time on ambulatory patients. Thus, a diet calculated for a person supposed to weigh 60 Kg. permits daily 60 Gm. of protein and altogether six to eight calories per Kg. body weight. Such a diet would actually consist of one egg and one ounce of bread for breakfast; one egg and four ounces of the low caloric vegetables for luncheon; a cup of broth and three ounces of lean meat and four ounces of vegetable for dinner. There is no doubt that enforcement of these limitations over a period of ten weeks can produce a weight loss of 37 to 42 pounds, but the claim that patients maintain their weight after termination of this dietary experiment is completely at variance with our own experience. Actually, the weight loss achieved by such near starvation procedures is not necessarily commensurate with the hardship involved and is moreover likely to yield to a rapid gain in weight as soon as the diet is interrupted. It is understandable that the majority of obese patients refuse to follow such a diet for an extended period of time (Rony 21).

Based on such observations, it has been suggested to substitute for starvation, a diet high in proteins but low in carbohydrate and fat content which is supposed to be tolerated well without emotional strain and yet produces satisfactory reduction of weight. The high protein diet is meant to allow quantitatively practically unlimited food intake and does not expose the patient to nitrogen deficiency or inadequacy of vitamin intake. It is regrettable that there are patients who do not lose weight according to prediction on the high protein diet even if the total caloric intake is restricted to 1000 calories per day. On the unlimited protein diet, the number of such refractory patients must be correspondingly greater. Denial of failures does not eliminate them from consideration nor are the facts explained away by the facile generalization that all these patients violate their diet.

It is true that there are obese people who, anxious though they are to lose weight, are unable to observe dietary restrictions; this lack of will power, according to prevailing opinion, is due to psychological causes. For those who assume that overindulgence in food is the sole cause of obesity, it seems clear that the essential pathogenetic factors are of an emotional nature. This belief seems to be borne out by the observation that people who are unhappy either lose their appetite or try to find solace in the consumption of more food. Hence, their gain in weight has been spoken

* From the Endocrine Clinic, St. Clare's Hospital, New York City.

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of as "anhedonic obesity" (Meyerson 18). It is also true and a matter of common experience that frustration or other complex and often obscure emotional factors can be translated by the patient into overindulgence in food irrespective of the coexistent desire to lose weight. Nevertheless, the claim of the psychological school that weight cannot be reduced unless attention is paid to the patient's emotional situation (Richardson 20) does not hold true; for over the past 15 years we have successfully reduced the weight of several thousand patients in our clinics; the mass attendance precluded any individual psychological attention, yet the therapeutic results obtained were satisfactory enough to cause a continued increase in the attendance of these clinics. It is equally impossible to agree to another generalization, namely that the frequent coexistence of obesity and neurosis should be interpreted in the sense that the obesity is a manifestation of the neurosis, for the latter causes excessive food intake and hence gain in weight. It is far more common in our observation that the neurotic state develops as a consequence of the obesity because the latter, especially if combined with undesirable fat distribution and other disfiguring changes of appearance (hypertrichosis), is quite likely to induce emotional instability. The obese, neurotic woman is unsociable, quarrelsome and hard to live with, yet she changes into a nicer, more livable and socially acceptable person after reduction of her excessive weight. Thus it is putting the cart before the horse to claim that the coexistence of these two conditions establishes the neurosis as the cause and obesity as the consequence.

Contrary to earlier assertions in the literature, based on thorough studies on a limited number of patients, that the obese do not deviate essentially from the normal in respect to their metabolism (Newburgh 18), a detailed study of a large obese population has revealed a metabolic pattern which deviates to a statistically significant degree from the normal mean (4). These deviations are most conspicuous in patients whose fat distribution is localized to typical areas of the body. Various stigmata indicative of endocrine disorders are usually associated with abnormal fat distribution.

The association of obesity with an endocrinopathy obviously is no proof of a causal relationship, for the abnormal nutritional state is likely to affect the function of the endocrine glands and account for symptoms of a secondary endocrinopathy. This interpretation of the sequence of events, however, is at variance with the facts for the onset of endocrine symptoms usually precedes the gain in weight. A further bone of contention is the frequency of endocrinopathies in the obese. According to the caloric school this coincidence is unusual and unrelated to the problem of obesity. Apparently, only those extreme instances of endocrine disorders are recognized by the energetic school which do not permit any other interpretation. This may include cases of acromegaly, myxedema, dwarfism and perhaps the adrenogenital

syndrome. The manifold manifestations of pituitary deficiency, however, with their unquestionable relationship to genital function, carbohydrate and fat metabolism, water retention, etc., are consistently ignored (5).

On the basis of the preceding discussion, the treatment of obesity should be planned separately for those whose caloric intake is above the average and for those who do not overeat. The overeating group should be sub-divided again according to the motivating forces, for the cause of overeating may be simply a habit or may be psychogenic or due to pathological influences.

The habitually overeating person should be systematically educated to control himself and change to reasonable dietary habits. If overeating is a consequence of emotional difficulties, the situation should be dealt with by appropriate psychotherapy. In both cases, patients must be induced to acquire sensible ways of eating. Such voluntary restriction of food intake need not approach the starvation level, especially if the protein content of the diet is sufficiently high. The glutton who consumes 4,000 to 5,000 calories a day loses weight readily if the food intake is restricted 30 or 50 percent, in other words, to a level of average food consumption. Educational measures as well as psychotherapy, however, often need support by procedures which help to curb the patient's appetite. This purpose is well served by the use of amphetamine sulphate in doses of five to ten mg. t. i. d. Adverse reactions such as insomnia, nervousness, headaches or cutaneous manifestations rarely call for termination of this medication. Another useful procedure is sedation with a mixture of atropine sulphate 1/300 to 1/200 of a grain with 1/4 to 1/2 grain phenobarbital t. i. d. alone, or in combination with amphetamine.

An abnormally increased appetite, however, is not always a mere habit or the manifestation of emotional difficulties, for it may express some organic disease. Thus the appetite of the diabetic is often enormous and his overconsumption of food helps to maintain or even increase his weight. Similarly, hyperthyroidism is often associated with increased appetite and the large consumption of food successfully copes with the patient's excessive catabolism. Of even greater practical importance is the abnormally increased appetite observed in case of hypoglycemia; the postprandial fall of the blood sugar elicits the sensation of hunger and almost insatiable craving for carbohydrates.

The abnormal appetite referable to diabetes or hyperthyroidism does not need elaboration in the discussion of the therapy of obesity. Management of hypoglycemia, on the other hand, is of particular importance, for no cooperation can be expected from a patient whose blood sugar is permitted to fall to a low level; his craving for carbohydrates cannot be conquered by will power. Such patients must be given frequent meals preferably every three hours, with complete elimination of sugar and all high caloric carbohydrates. Thus the diet consists essentially of proteins, the five and ten per cent vegetables and fruit.

The use of amphetamine and sedation also is effective in this group of patients.

After elimination of the overeating patients, a large number of people are still left who seek the help of the physician because they cannot control their weight though their consumption of food is not more, or in some cases even less, than the calculated requirements. Successful therapy of this group depends upon analysis of their metabolic status and the function of their endocrine system if starvation procedures are to be avoided. The abnormal metabolic pattern of these patients consists of a series of deviations from the normal which may be present completely or only partly. There is no one of the findings which by itself would either explain the development of obesity or permit any conclusions as to its pathogenesis. The total of these deviations, however, characterizes the people whose general metabolic activities are abnormal in the sense of permitting greater savings of energy and storage of saved up food in the form of fat. This characteristic pattern consists of an almost normal or low basal metabolic rate; a decrease or absence of the specific dynamic action of proteins; an increased sugar tolerance, occasionally with a low fasting blood sugar but more often with a late hypoglycemic drop; an increase of blood uric acid, cholesterol, and not infrequently, chloride and sodium values; the salt tolerance test shows retention of both salt and water; a lymphocytosis and a moderate eosinophilia are common and can be interpreted, according to recent experimental studies, as an expression of deficient adrenotropic activity of the anterior lobe (Thorn et al. 23). X-ray studies of the cranium reveal cranial dysplasia of the type described as characteristic of pituitary disease and occasionally abnormalities of the sella turcica (6).

In the course of the physical examination, stigmata of endocrine disorders, and particularly of hypothyroid or pituitary insufficiency should be looked for. Thick, coarse and dry integument, fat pads in the nape of the neck and dry coarse hair on the head are indicative of the former while fat distribution in the peripelvic region or on the inner aspects of the arms and thighs suggest the latter. Hypoplasia or functional disorders of the genital organs are corroborative evidence in favor of the pituitary disorder. Rarer forms of endocrine obesity such as the hyperadrenocortical type or the obesity of the castrate are readily diagnosed on the basis of the patient's history and appearance.

Among the clearcut endocrinopathies, hypothyroidism is seldom responsible for an exaggerated gain in weight. The myxedematous patient is not necessarily overweight and his excess weight is essentially due to water retention which is rapidly disposed of upon administration of thyroid extract. Hypometabolism, however, is noted in many obese patients in the absence of clinical evidence of hypothyroidism. Hence we must distinguish between the hypometabolism of the obese patient with and without hypothyroidism. A decrease of the basal metabolic rate, of course, is not a specific manifestation of thyroid deficiency, for other hor-

monal factors besides the thyroid hormone (e. g., several of the anterior pituitary hormones), are capable of increasing oxygen consumption. Adrenalin, the hormone of the adrenal medulla is another known metabolic stimulus. Actually, hypometabolism in the obese expresses more often a hypofunction of the pituitary rather than of the thyroid.

The hypothyroid, obese patient should be given thyroid extract but it must be borne in mind that the tolerance of the patient whose thyroid gland is not efficient is less than normal. In view of the fact that the substitution requirement of the myxedematous patient does not exceed two, or at most, three gr. of thyroid substance, the non-myxedematous hypothyroid patient does not need heavier dosage, and may react with tachycardia or nervousness to any further increase. This tolerance is in startling contrast to the high tolerance observed in cases of hypometabolism of non-thyroid origin. Thus, determination of the basal metabolic rate is not an accurate guide for thyroid therapy. It is simpler to judge the response of the patient by weight loss on the one hand and the cardiac reaction on the other. If the weight loss is not enough on the initial dose of one grain a day, increments of one grain should be given, provided the pulse rate does not increase. Upon exceeding tolerance, it is best to discontinue the medication completely and not to resume it until the pulse slows down to an acceptable level.

Thyroid medication in the non-hypothyroid patient requires less caution. As long as the weekly weight loss of two and one half to three pounds is attained without the thyroid extract, medication should be postponed until the weight loss slows down below expectation. Then thyroid medication is started with one grain daily and increments of one grain are added as required for the progress, provided the thyroid effect is well tolerated. If the weight loss is not adequate on a level of five or six gr. daily, it is unlikely that increased dosage will give better results. Such patients apparently eliminate the thyroid substance without utilizing it.

The sensitivity to the thyroid hormone can be increased if organic potassium compounds such as potassium gluconate are given in seven and one half gr. doses, four to six times daily; a seven per cent potassium acetate solution, one tablespoonful, t. i. d. is even more effective. In stubborn cases, ephedrine sulphate, 3/8 gr., once or twice daily or the injection of a foreign protein (bacterial vaccine) can be tried to augment the response to the thyroid hormone.

Nervousness observed in the course of thyroid therapy may be due to the apprehension of the patient who bears a prejudice against thyroid medication or it may be due to overdosage. Mild sedation with a mixture of atropine-phenobarbital usually dispels the symptoms but if the response to sedation is not prompt, it is best to discontinue the medication and start it again on a lower level after all symptoms have subsided.

Patients with clinical symptoms pointing to dysfunction or insufficiency of the pituitary gland should be treated symptomatically (7). Among the common metabolic disorders, hypometabolism and hypoglycemia require administration of thyroid extract in the former and an antihypoglycemic diet in the latter case.

The value of pituitary extracts in the therapy of obesity has been questioned mainly because weight loss can be obtained without any glandular therapy and particularly, because disorders of the menstrual cycle in the obese also improve without organotherapy once the reduction of weight has been accomplished. Another objection is based on the failure of pituitary therapy observed by certain investigators. The latter, of course, may well be due to the use of inert pituitary preparations. The principle of therapy, however, is based on a number of well established facts as follows:

1. Gonadotropic therapy of menstrual disorders independent of obesity is recognized as a successful procedure;
2. Combination of gonadotropins with an unfractionated pituitary extract or one of the metabolic factors of the pituitary gland augments the gonadotropic effects (12); hence a combination of gonadotropins with such a synergistic extract is justified just for the treatment of the menstrual disorder;
3. Irrespective of their gonadotropic effects, pituitary extracts are useful for metabolic purposes such as:
 - a. Prevention of the loss of liver glycogen by their glycostatic effects which counteract hypoglycemic tendencies (8);
 - b. The increase of the specific dynamic action of protein apparently by stimulation of hepatic function (11);
 - c. The direct effect upon fat metabolism: pituitary extracts rich in growth factor produce a rise of ketones in the blood and urine (Lee 14, Long 17). The increased breakdown of fat reaches its maximum 12 hours after injection and lasts for 18 to 24 hours.

The normal or the overeating, obese person responds with an increase of ketone bodies in the blood to the ingestion of a fat meal. No such rise occurs in the obese whose fat distribution is of the pituitary type (10);

Injection of a crude pituitary extract into normally fed rats accounts for a substantial (41 per cent) reduction of body fat as compared with the pair-fed controls (Lee and Shaffer 16).

Injection of a pituitary extract causes mobilization and transport of fat to the liver, as indicated by the use of deuterium tracers (Barrett et al. 1).

The hypophysectomized animal loses less fat than the control, though both are fed the identical low caloric

diet. This shows that the ability to mobilize fat is reduced (Lee and Ayres 15). The same point is proven by experiments on hypophysectomized rats which can be maintained on a practically pure fat diet without evidence of hypoglycemia, whereas the blood sugar falls rapidly on fasting the same animal. Thus, the hypophysectomized rat can metabolize ingested fat but cannot mobilize it, even in an emergency, from its own depots (Samuels 22).

These effects can be demonstrated by biochemical methods; additional effects are corroborated by the clinical experience on obese patients whose fat distribution after treatment with pituitary extract is closer to normal than before treatment. The redistribution of fat is quite obvious to the patients who notice differences of their circumference out of all proportion to their actual loss of weight. Even after the weight reduction has terminated and a steady weight is maintained, measurements, as indicated by the patient's clothing, still continue to recede.

In patients whose fat distribution is of the pituitary type and who present clinical signs of a pituitary disorder, the retention of salt and water is often conspicuous (pituitary retention syndrome 9). Though salt and water retention occurs also in hypothyroidism or in obesity without clinical evidence of pituitary disease, this metabolic abnormality usually indicates a functional impairment of the pituitary. A common cause of the disorder is the presence of a small adenoma within the anterior lobe which presses upon both the anterior and posterior lobes. The scope of weight gain due to water retention is illustrated by the sudden increase (sometimes up to 10 pounds) experienced by many women preceding menstruation. Some or even all of the retained water may remain in the body postmenstrually and result, in the course of time, in an enormous accumulation of tissue water.

The predominant role of water retention in the pathogenesis of obesity can be suspected if the patient admits that instances of sudden gain in weight have occurred repeatedly. In the absence of such clinical evidence, retention should be suspected in the presence of oliguria, though the urinary volume is normal or even increased, in case the daily liquid intake is exceeded by the output. Oliguria or positive water balance require a determination of the salt tolerance which frequently reveals that the major part of the test salt and a variable amount of water is retained whereas the normal person eliminates the test salt almost quantitatively with a commensurate increase of water excretion. Comparison of the result of the salt tolerance test with blood levels of chloride is not always consistent. It is more likely that current studies on blood sodium values will show better agreement with the findings of the salt tolerance test.

Once salt and water retention has been demonstrated, the obese patient must be enjoined to refrain from the ingestion of salt as far as feasible. Spices of vegetarian origin, however, are permissible. Liquid intake should be restricted to 1,500 cc. or less per day. These restrictions are combined with medication

to eliminate retained sodium. Two to three grams of ammonium chloride per day is an effective agent used alternating with organic potassium salts, aminophyllin or Theocalcin in preference to the mercurial diuretics.

Administration of posterior pituitary extract serves the same purpose. The anti-diuretic effect of the posterior pituitary hormone is followed by a diuretic phase which is associated with substantial excretion of sodium chloride. Thus, injection of posterior lobe extract at intervals of two to three days is useful in reducing sodium and water retention. The initial dosage is five minims; increments of one minim each time up to 10 minims are given unless abdominal cramps indicate that tolerance has been exceeded; one minim less constitutes the maintenance dose.

The posterior pituitary extract can be combined with the anterior lobe extract and given jointly two or three times weekly. In the male or in the normally menstruating female, an unfractionated pituitary extract should be used, preferably one rich in the growth promoting factor. The use of such extracts is safe and entails no complications except for an occasional prolongation of the menstrual cycle. In case of menstrual disorders, it is useful to fortify the unfractionated pituitary extract with chorionic gonadotropin; small doses of the latter (100 U.) being used in the first half of the cycle for stimulation of the follicles whereas a larger dose (200 to 300 U.) is given during the second half of the cycle to promote lutein body activity.

Adrenocortical obesity is not suitable for medical therapy. The nature of this endocrine disorder requires surgical intervention, i. e., removal of the cortical tumor or resection of the hyperplastic adrenals. Such an operation, if successful, accomplishes not only a cure of the endocrine manifestations of the disease but also causes a rapid loss of weight without particularly stringent dietary restrictions. In less serious cases of adrenocortical disease, when surgical interference does not seem to be warranted, the chances of controlling body weight are not good.

Obesity associated with castration or menopause also deserves discussion. The causal relationship between castration and accumulation of fat is well known though the mechanism is still in doubt. The decreased physical activity of the castrate is most probably contributory but the disturbance of the endocrine equilibrium and subsequent metabolic abnormalities are too well established by experimental evidence to be dismissed lightly. Unfortunately, the administration of sex hormones is no cure of the

postcastrational obesity, for it does not markedly alter body weight or fat distribution. Sex hormone therapy is far more effective if used in time for the prevention of the untoward fat deposits.

The situation, quite similar in the menopause and the male climacteric, has been far better studied. Castration or decline of gonadal hormone secretion is almost invariably associated with accumulation of fat in the abdominal and pelvic region. Once the fat is deposited, it is rather difficult to make it disappear either by the dietary approach or even by a combination of the former with adequate hormone therapy. If sex hormone treatment is instituted upon the onset of menopause, the accumulation of fat deposits can be prevented, particularly if sensible dietary restrictions are adhered to.

The protruding abdominal fatpad of the elderly male does not respond satisfactorily to weight reduction with or without sex hormone therapy. One reason of this failure is the accentuated lordosis so common in the elderly male; the abnormal posture accounts for the protrusion of the abdomen which emphasizes the extent of the abdominal fat pads. Correction of the posture is the best way to relieve the unsightly protuberance. Accumulation of abdominal fat, however, persists in almost all elderly males even though they are not overweight and in spite of what would seem adequate physical activity. The independence of the abdominal fat tissue from the influence of the general metabolic status is comparable to that of lipomatous tissue and has been convincingly demonstrated by transplantation experiments (Hoffmann 13).

SUMMARY

The inconsistencies of the caloric and psychogenic interpretation of obesity are pointed out.

Different treatment is needed by patients who overindulge in food and those who do not overeat. The first group requires education or psychotherapy and occasionally, help by sedation and amphetamine.

The metabolic causes of an increased appetite should be investigated and corrected.

If the food intake is not excessive, evidence of an endocrine disorder, especially a functional deficiency of the pituitary should be looked for.

A treatment is outlined, consisting of moderate dietary restrictions and the use of thyroid, mild diuretics and pituitary extracts.

Evidence for the value of pituitary therapy is reviewed.

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Small Intestinal Deficiency Pattern: Current Status

By

W. H. GLASS, M.D.

HARTFORD, CONN.

IN THE FALL OF 1941, Lepore and Golden (1a) and Golden (1b) reported on a clinical syndrome due to "deficiency of the Vitamin B Complex." They described a series of cases with deficient dietary intake who manifested a syndrome of weight loss, asthenia, anorexia, irritability and personality changes, and vague gastrointestinal complaints with objective findings of flat oral dextrose tolerance curve, abnormal small intestine roentgen ray appearance, malnutrition, hypochlorhydria or achlorhydria, increased capillary fragility and absence of clinical features of idiopathic steatorrhea or pellagra. The variations in the pattern of the small intestines, particularly the jejunum, are reproduced, and the response to oral or parenteral B Complex is detailed.

In the past decade, increased cognizance of organic and functional changes in the small intestines has led to numerous investigations along this line. With careful roentgen ray technique the small intestinal mucous membrane, with few exceptions, can be as adequately visualized as the stomach or the colon. The technique of the roentgenological examination of the small intestines is essentially that outlined by Buckstein (2). Basically, the procedure has to be individualized. The routine here is, following adequate projection of the stomach and duodenum, to take Bucky films of the jejunal coils on a fifteen minute interval schedule for two to three hours. These are developed immediately and seen wet by the examiner. The interval between the films is shortened or lengthened depending on the appearance of the small intestinal coils. With the exception of the first series done, the procedure is ordinarily stopped at the end of two to three hours with the beginning of the filling of the ascending colon.

Mackie (3) in 1933 is credited with the first description of the functional changes in the small intestines. This and subsequent reports (4, 5, and 6) during the next few years dealt primarily with descriptions of sprue and spruelike entities (nontropical sprue, idiopathic steatorrhea, and celiac disease). Fur-

ther investigation (5, 6, 7 and 8) has led to the assumption of the identity or very close relationship of these diseases.

There is included with this report several reproductions of the small intestinal changes referred to. Advanced changes (Figure 4) with almost total loss of mucosal pattern, dilatation and almost invariably gas and fluid levels have been aptly described by Kantor (9, 10) as the "moulage sign." He points out that this can be sufficiently extensive to be confused with the radiographic pattern of adynamic ileus. These advanced changes are readily recognizable and have been proven by postmortem examination to represent marked mucosal atrophy, loss of normal valvulae conniventes, with microscopic indication of chronic low grade inflammatory changes.

The evaluation of less extensive changes and correlation with pathological findings is much more difficult. Primarily, people with observed minor changes infrequently come to postmortem examination. If observed changes were limited to small areas in the living, their exact location may not be found at necropsy. Poppel and Herstone (11) have shown the impossibility of radiographically determining the distance of any small intestinal lesion from the duodeno-jejunal junction from its location in the abdomen, except for those obviously very near the duodeno-jejunal junction.

Correlation of less extensive changes with demonstrable physiological and biochemical variations has been fully investigated. It has been recognized early (12) that nonenteric disease associated with hypoproteinemia or adequate variation in albumin globulin relationship can produce this radiographic pattern. It also has been shown, as cited by Golden (1b), that the roentgen projection of the small intestinal pattern of experimentally hypoproteinemic dogs (13) cannot be differentiated from animals with extensive B deficiency but adequate blood protein content (14). Krause and Crilly (15) include diabetes insipidus, parathyroid disease, hypocalcemia, and allergic states amongst the systemic diseases which give this pattern.



Figure 1. — Normal small intestinal pattern. Fine, feathery appearance of mucous membrane with distinct delineation of folds.

Marked emotional upsets have been seen as a basis for this picture (16). Golden (16 and 1b) has postulated the entire mechanism to be based on alteration of the complex intramural nervous system of this portion of the gut. It is well known that normal newborn infants have an identical pattern. The lack of myelinization of nerve fibers in early life would tend to substantiate this postulate. The findings in hypoproteinemia have been thought to be on the basis of mucosal and submucosal edema. I have been unable to find any report of a similar picture in right sided heart failure. In a limited number of cases with right sided heart failure, studied by me, the pattern was not demonstrable.

The pattern in diabetes insipidus is again presumably on the basis of submucosal edema. The burden of proof remains on those who postulate this idea. Edema is not generally acknowledged to exist in diabetes insipidus. On the contrary, dehydration is ordinarily found.

Hypocalcemia producing this pattern can be difficult to interpret. In sprue (nontropical sprue, celiac disease) the prime site of disease is in the wall of the bowel and there is faulty absorption of all elements, particularly fatty acids and fats. The fatty acids combine with intraluminal calcium to produce insoluble calcium soaps which are carried away in the fecal stream. In addition, as pointed out by Peters and Van Slyke (20), "the chief reason for failure to absorb calcium in the presence of fatty diarrhea appears to be deficiency of Vitamin D, which cannot be absorbed without fat." A similar process occurs in a deficiency of pancreatic lipase. The production of sterols from fatty acids is incomplete. Combination with calcium to produce soaps occurs and a calcium deficiency results. The converse, that a primary cal-



Figure 2. — Early changes. Segmentation with areas of hypo and hypertonicity in the jejunum. There is a loss of continuity of the intestinal coils, ileum normal.

cium deficiency, be it nutritional or metabolic, produces this intestinal pattern, has been incompletely proven. The altered jejunal pattern has not been observed in primary pancreatic deficiency, despite grossly lowered blood calcium levels. The role of ionized calcium as a nervous mediator and its action as a neuromuscular sedative is well known. Its exact application in Golden's (1b) postulate has not been completely evaluated.

In a study (17) done in a tuberculosis sanitarium this radiographic picture was found only in 17% of those patients with sufficient gastrointestinal complaints to warrant investigation. This despite observation of individuals preterminally with advanced cachexia from pulmonary disease or miliary tuberculosis where the food intake had been essentially nil for protracted periods.

In 1927, well prior to the recognition of this radiographic entity Morse and Cole (18) called attention to the variations in the caliber of the small gut associated with irregular emptying of the stomach. Subsequent to observations made by many investigators during the '30's and early '40's the following specific diseases of the gastrointestinal tract (15), exclusive of the deficiency states were reported to contribute to a similar radiographic pattern: peptic ulcer, upper gastrointestinal cancer, tuberculosis of the small intestines, biliary or pancreatic disease, chronic ulcerative colitis, regional ileitis, and sclerosing inflammation of the mesenteric lymphatics.

Adlersberg (21) notes that a similar pattern is found following the administration of morphine or by the addition of oil to the barium suspension.



Figure 3. — Advanced changes. Large sausage-shaped areas of small bowel, with almost complete obliteration of mucosal pattern. Early involvement of the ileum.

Ruffin, Baylin and Cayer (22) acknowledge the fact that small intestinal pattern alteration is common in sprue and frank deficiencies of B Complex, but feel that the radiographic alteration may occur in apparently normal individuals. They caution against interpreting minor changes as significant. Kiefer (23) feels that Ruffin et al have not made adequate allowances for normal variations and that some of the "mild" and "moderate" changes they demonstrated should be classified as normal variants. Nevertheless, they have certainly demonstrated some significant abnormality in apparently intact individuals. In one instance, there appears to be a definitely abnormal intestinal pattern which nine months later returned to normal without any intervening therapy or change in mode of living.

I have recently reported a series of cases (19) in which the gastric outlet, pylorus or surgical stoma, was so affected as to open irregularly and produce a varied bolus size which resulted in a radiographic pattern indistinguishable from that under discussion. In none of these instances was there any response to adequate B Complex therapy. Some did respond to surgical procedures with a return of the radiographic pattern to normal.

In his monograph Golden (24) prefers the use of the term Disordered Motor Function to Small Intestinal Deficiency Pattern in describing this radiographic alteration, so that the multiple etiologic factors, as detailed, would be included. Certainly this terminology is preferable.

The question has been frequently raised and never satisfactorily answered as to whether a B Complex deficiency producing this pattern is an early, easily



Figure 4. — Far advanced changes. Total obliteration of mucosal pattern. Marked segmentation extending well into the ileum. Small areas of fluid levels do not reproduce satisfactorily on this photograph.

reversible stage of idiopathic steatorrhea, or an independent entity. In cursory investigative work here, we have been unable to find any individuals who present this pattern, and who respond promptly and completely to oral and peroral B Complex, with a normal fat stool content. The fat stool content done here is evaluated by weight of the dried three day stool collection with the patient on a standard Schmidt pancreatic test diet, yielding 132 Grams of fat per day. Results are briefed in the accompanying table. To be noted is the fact that this is most frequently found in the female. With the exception of the man cited in the table, all other males presenting this pattern were excluded because of demonstrable mechanical factors. I have been unable to find reports of more detailed evaluation of stool content in this illness. On the basis of findings in a small group of cases one concludes that the entity of the small intestinal deficiency pattern is early reversible idiopathic steatorrhea.

CONCLUSIONS

Idiopathic steatorrhea and the disordered motor function of the small intestines, if it be on the same basis, respond to B Complex. Depending on the intensity of the illness, other therapeutic measures as dietary alteration to give adequate caloric intake of assimilable foods; Vitamin D in non fat vehicle, and parenteral calcium, if an insufficient amount is absorbed, are, of course, indicated. The basic disease, however, is the alteration of the jejunal mucosa by deficient intake of some factor or factors in the whole B Complex. Other therapy is indicated to treat the bodily changes subsequent to the altered absorption of intestinal contents.

TABLE I

Age Sex	Diet	Emotional Background	X-ray	Weight Three Day Dried Stool	Rx	Results
F 42	grossly deficient	unstable food fadist	advanced changes	140 G	IM and oral B Complex Food increase	Fair
F 26	deficient	stable voluntary weight re- duction	moderate changes	100 G	oral B Complex	Good
F 32	deficient	stable	moderate changes	106 G	oral B Complex	Good
F 54	grossly deficient	unstable	moderate changes	130 G	IM and oral B Complex	Good
F 58	deficient	stable	advanced changes	130 G	IM and oral B Complex	Good
F 62	apparently adequate	very unstable	advanced changes	180 G	IM and oral B Complex	Good
F 31	deficient high CHO	stable obese	moderate changes	120 G	oral B Complex	Fair
F 36	deficient high F and CHO	stable obese	moderate changes	105 G	oral B Complex	Good
F 18	deficient	stable	moderate changes	114 G	oral B Complex	Good
M 32	deficient very high CHO	stable obese	advanced changes	164 G	IM and oral B Complex	Good

Grossly visible steatorrhea only occurs where there is extensive fat and soap content in the stool. In cases studied here, all who demonstrated significant mucosal changes in the jejunum, presented steatorrhea on chemical analysis of the stool. It is concluded that idiopathic steatorrhea is the more advanced phase of so called B Complex deficiency intestinal pattern. This latter term should no longer be used and Golden's (24) terminology of Disordered Motor Function with

a subdivision as to its etiological basis is much the preferred terminology.

SUMMARY

A brief review of the literature referable to small intestinal mucosal changes is given. Cases of so called deficiency pattern studied here have all proven to be due to a deficiency of some factor or factors in B Complex. The term Small Intestinal Deficiency Pattern should be discarded and the term Disordered Motor Function with its etiological basis used instead.

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Steatorrhea in Diabetes Mellitus

By

HENRY FIELD, JR., M.D.,
NIELS C. KLENDSHOJ, M.D.

and

BRYON D. BOWEN, M.D.*

BUFFALO, N. Y.

STEATORRHEA has not frequently been recognized in association with diabetes mellitus but the occurrence may be more common than has been appreciated. There may be a common etiology in primary disease of the pancreas or, as appears to have been the situation in the case to be presented, steatorrhea may be due to depression of the external secretion of the pancreas by the metabolic disorder which is present in uncontrolled diabetes. Jones, Castle and Mulholland (1) discussed the possibilities that diminished proteolytic and lipolytic activity might explain intestinal symptoms in severe diabetes and the inability of some diabetics to progress satisfactorily on a given diet.

It has become apparent, as will be discussed, that steatorrhea may easily miss detection. It may occur in an important degree without diarrhea and without the traditionally characteristic appearance of "fatty stools." It may fail to be demonstrated by the simple staining of a stool specimen with Sudan III.

Steatorrhea and diabetes mellitus were reported in a case of carcinoma of the pancreas by Urmey, Jones and Wood (2). Marble (3) reported that among 10,000 cases of diabetes, 33 patients had primary carcinoma of the pancreas. In only three instances was it noted that the stools were of the type suggesting pancreatic insufficiency but he remarked that the records may not have been complete on that point.

Glycosuria was said to have been reported only six times among 65 operated cases of pancreatic cal-

culi collected from the literature up to 1938 by Haggard and Kirtley (4). They stated that frothy, ill-smelling stools were rarely reported in those patients. They also noted that weight loss and even emaciation was present in 75% of the operative cases and even more frequently in the 139 non-operative cases.

Since that time, many more cases of diabetes mellitus in association with calculi or calcification of the pancreas have been reported and several cases have also had steatorrhea. Snell and Comfort (5) reported that diabetes, actual or latent, was present in eight cases and that steatorrhea occurred eight times among 18 patients with pancreatic calculi. King and Waghelstein (6) reported diabetes mellitus in two patients and latent diabetes in a third with calcification of the pancreas. The stools of their patients were said to have been normal in appearance but fat was demonstrated in the stools of two of them by staining with Sudan III. Two of the four cases of pancreatic achylia and steatorrhea of Beazell, Schmidt and Ivy (7) had diabetes. One of these patients had calcification of the pancreas. Cases of calculi of the pancreas with diabetes and steatorrhea have been reported by Thomsen (8) and by Rockwern and Snively (9). The data presented do not establish the etiology of the steatorrhea in the diabetic of Escudero and Espejo Sola (10).

CASE REPORT

L. R., male, 40 years, was admitted to the hospital November 19, 1944. He had had a heavy glycosuria and a fasting blood sugar of 211 mg. per 100 cc. when he was in the hospital with lobar pneumonia in April of 1940. After receiving small doses of insulin for four days his blood sugar was 116 mg. per 100 cc., one hour after a breakfast which had been preceded by a dose of six units of regular insulin. During the remainder of that

*From Buffalo University, School of Medicine, and the Buffalo General Hospital.

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hospitalization he took an unrestricted diet without having glycosuria.

Six weeks before his last admission, glycosuria was discovered at an examination requested because of great fatigue. He had lost 25 pounds in two years but had noted no more than his usual large fluid intake. Five weeks before admission he had had a transient edema of the ankles. His glycosuria was not controlled by diet and insulin and he developed aching pains in his legs.

He was malnourished. He had severe dental caries and pyorrhea. His liver was enlarged to half way to his umbilicus. Knee jerks and ankle jerks were absent. A few days after admission he developed a severe hyperesthesia of his feet.

Stools were of normal number and appearance. The first stool specimen to be stained with Sudan III was reported to contain no fat. Subsequent specimens contained numerous irregular flakes which stained red with Sudan III only when they melted into globules on heating. Analyses of the fat contents of the stools for four day periods, collected between markers of carmine, during the testing of regimens of pancreatin therapy are shown in Table I.

An X-ray examination of the abdomen showed no calcification in the region of the pancreas and that of the chest was normal. Basal metabolic rate was -5%. Duodenal fluid showed no lipolytic activity on January 12, 1945. Lipase was present in the duodenal fluid on June 1, 1945.

His weight, on admission, was 116 pounds. It remained at about that level during the first three weeks. During that time he was taking only from 1400 to 1800 calories of his prescribed diet of C 180, P 90 and F 110. Subsequently he ate most of his diet which was then increased to C 250, P 90 and F 120. He remained aglycosuric, or nearly so, but during his fourth, fifth weeks in the hospital his weight decreased from 116 to 110 pounds. It remained at approximately that level during most of the time of collection of stool specimens. Thereafter, he continued to take three grams of enteric coated tablets of pancreatin with each of his four meals. His weight increased to 114 pounds before he left the hospital. On May 24, 1945 he weighed 130 pounds. The use of pancreatin was discontinued after the demonstration of lipase in his duodenal fluid on June 1. His weight continued to increase and on September 13, 1945 was 139 pounds.

COMMENT

Steatorrhea was associated, in this case, with a temporary failure of demonstrable lipolytic activity in his duodenal fluid. Lipase was subsequently found to be present in it. No calcification in the pancreas was demonstrated by X-ray. There were no signs or symptoms suggestive of inflammatory disease of the pancreas. It may be presumed that the reversible depression of the lipolytic activity of the pancreas was secondary to the metabolic disorder of uncontrolled diabetes. The severity of the metabolic disorder in this case was indicated by the enlargement of his liver, which subsided promptly, and also by the neuritis, the symptoms of which became severe shortly after his admission to the hospital.

The possibility of such depression of the external secretion of the pancreas was demonstrated by the work of Jones, Castle and Mulholland (1) who studied the pancreatic enzymes in the duodenal fluid of 68 diabetics. 33% of them had proteolytic activity below normal standards and 37% had decreased lipolytic activity. In only one patient was none demonstrated but in five patients there was very little lipo-

lytic activity in the duodenal fluid. In five patients whose duodenal fluids were studied during acidosis and after recovery from it there was an average increase of 85% in the lipolytic activity.

Since the above case was studied, we have observed three other diabetics who failed to gain weight while they were aglycosuric and were consuming diets approximating 45 calories per kilo per day. It was not feasible to have quantitative determinations of fat in the stools of those patients but, an abnormal amount of fat was seen in the stools of two of them after staining with Sudan III. It is known that steatorrhea may fluctuate widely and it is possible that abnormal amounts of fat might have been found in the stools of the third patient if more specimens had been stained or if they had been subjected to chemical analysis.

None of these patients with steatorrhea had diarrhea or abnormal appearing stools. The normal appearance of the stools of King and Waghelstein's (6) two patients with steatorrhea has been noted. The correct diagnosis in a case of sprue, studied by one of us, was first suspected following an attack of tetany. Her complaints were abdominal distension and weight loss. She had normal appearing stools despite a total fat content of 51.6% of their dry weight.

Furthermore, steatorrhea can not always be demonstrated by simple microscopic examination of a specimen stained with Sudan III. Such examinations were made and reported to be negative in the case reported and the case of sprue mentioned above. In the stools of those two patients there were irregularly shaped, flat particles larger than the usual fecal debris. It might have been suspected that those particles were fatty acids or fat but they were not stained by Sudan III until the slide had been heated. Then those particles were replaced by red-staining globules.

Black and Fourman (11) reported the physical and staining characteristics and the chemical analyses of 150 stools from patients with sprue or suspected of having sprue. Out of 102 stools with fat content of more than 25%, only 51 were definitely pale. In another report (12) they stated that half of the stools with a fat content of more than 25% of the dry weight were found to be well colored. They attributed the paleness of stools in sprue to reduction of stercobilin to stercobilinogen. They said that when pale stools are treated with acid alcohol for an hour or two, the alcoholic extract is colored.

Black and Fourman (11) also reported that fatty acid crystals were detected in only 46 of the 102 stools with a fat content of over 25% and that steatorrhea can be detected with certainty in all cases only by chemical analysis.

Cooke and his associates (13) reported on fat balance studies in 29 cases of idiopathic steatorrhea. They encountered many more such cases than had been anticipated. They noted that the stools of many of their patients were of normal color and consistency. They also found that microscopic examination for fatty acid crystals was unreliable.

The stool analyses (Table I) in this case appear to indicate that enteric coated pancreatin was effective substitution therapy and that powdered pancreatin was not effective. We would not draw conclusions as to the latter from one period because of the variability of fat utilization which will be discussed. Further studies were not feasible.

TABLE I

Treatment, 4 Day Periods	Enteric Coated Pancreatin Grams Daily				
	Control	Powdered Pancreatin, 24 Gms. Daily	24 Gms.	6 Gms.	12 Gms.
Feces, Neutral Fat, Gms.	44.5	53.3	8.8	15.0	8.9
Feces, Combined Fat, Gms.	9.5	5.7	7.6	35.5	4.3
Feces, Fatty Acids, Gms.	14	12.8	3.4	6.3	2.5
% Loss of Fat in Stools	76.4	79.8	22.0	63.2	17.4

It may be noted, however, that the stool analyses were consistent and the results conform with his weight curve. The utilization of 50% of the protein and 25% of the fat in his diet would have supplied him with approximately 25 calories per kilo per day. He maintained a constant weight of about 110 pounds during a period of observation when he was receiving pancreatin part of the time.

The reported findings concerning the need for substitution therapy and its efficacy in pancreatic insufficiency have not all been in agreement. Some patients, following resection of the head of the pancreas, have been reported to have normal or not seriously impaired fat absorption (14, 15).

Without considering the possibility of an accessory pancreas or the development of a fistula from the pancreatic remnant to the intestinal tract, such cases are understandable from reported experimental findings. Lipase is present in both gastric and intestinal secretions and in bacteria. Both digestion and absorption may be influenced by intestinal motility. It is doubtful if there is much absorption of fat from the colon (16) although hydrolysis of fat may continue there. Pratt and his coworkers (17) found that by small frequent feedings and attention to their general welfare, it was possible to obtain practically normal absorption of fat, without replacement therapy, in dogs deprived of their external pancreatic secretion. Since different dogs on the same diet and the same dog on the same diet at different times may absorb very different amounts, Handelsman, Golden and Pratt (18) concluded that unknown factors influenced the absorption of food.

A similar variability in defective fat absorption by humans was found by Black and his associates (19). They reported that, in their studies of sprue, the variation between successive four day stool collections was very great — so much so that they considered

all their results in terms of twelve day periods.

These disparities are explainable by the findings of Frazer and his associates which have contravened the established conception that fats must be hydrolyzed into fatty acids and glycerol before being absorbed. By simple but ingenious and decisive experiments they have shown that a large proportion of neutral fat, after being emulsified to a particle size of less than 0.5 μ , is absorbed without lipolysis (20, 21). Such particles enter the systemic circulation through the lacteals; are responsible for the normal post-absorptive lipemia and are deposited in the fat depots. Even unhydrolyzable liquid petrolatum was absorbed after being emulsified into particles of less than 0.5 μ size (22). Fatty acids are absorbed into the portal circulation and their early storage is in the liver.

Of the various combinations studied as emulsifiants, only the triple combination of bile salts/fatty acids/monoglycerids was found to be effective throughout the range of conditions obtaining in the small intestine (22). Only partial lipolysis is needed to provide the fatty acid and monoglyceride for this emulsifying system. It may be presumed that extrapancreatic lipases may effect sufficient lipolysis to supply the emulsifiants needed for more or less complete absorption of the remaining neutral fat in achylia pancreatica. It may be that the unusually large fat loss found in the stools of this patient was due to depression of the gastric and intestinal lipases in addition to that of the pancreas.

In animal experiments, Coffey, Mann and Bollman (23) found improvement in carbohydrate utilization but no significant effect on the utilization of protein or fat with the feeding of various preparations of the pancreas to depancreatized dogs. Selle and Moody (24) found good improvement in the utilization of carbohydrate and protein with the feeding of pancreatin but no improvement in the utilization of fat. They found no uniform significant difference between the action of coated (enteric) and uncoated pancreatin on the digestion of fat in their depancreatized dogs. The U. S. Pharmacopeia has standards for the ability of pancreatin to digest starch and protein but has no specifications for lipase content. Beazell, Schmidt and Ivy (7) found that, of eight products bought at local drug stores, two were essentially inactive.

Nevertheless, the seven cases of achylia pancreatica in whom substitution therapy has been studied in recent years (7, 14, 25, 26,) have all obtained good effects on the utilization of fat with the use of pancreatin. All of them were given enteric coated pancreatin.

The 24 grams of pancreatin used by Beazell, Schmidt and Ivy (7) was calculated, on the basis of assays of the pancreatin used by them, to represent only about 15% of the pancreatic juice normally secreted in 24 hours. They subsequently reduced the dosage to from 2 to 3.3 grams with each meal with satisfactory results as evidenced by subjective reactions and the character of the stool. In our patient, when the dose of pancreatin was reduced to 1.5 grams with each

of his four meals, there was a recurrence of steatorrhea. When the dose of pancreatin was increased to 3 grams with each meal there was again a good utilization of fat.

SUMMARY

A case is reported of self-limited steatorrhea in a diabetic, the severity of whose metabolic disorder was evidenced by a reversible enlargement of his liver and the acute development of neuritis. He had a temporary absence of lipolytic activity from his duodenal fluid without evidence of primary disease of his pancreas.

There was no diarrhea or abnormal appearance of

his stools. The fat in his stools was stained with Sudan III only after heating.

Stool analyses indicated a good improvement in his fat utilization with the use of enteric coated pancreatin.

In two of three subsequent patients with diabetes mellitus who failed to gain weight while they were aglycosuric and were consuming diets approximating 45 calories per kilo per day, excess fat was demonstrated in the stools by staining with Sudan III.

Neither the appearance of stools nor their microscopic examination may be relied upon for recognition of steatorrhea.

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NUTRITION

The Influence of Ascorbic Acid, Sodium Ascorbate, Calcium Ascorbate and Orange Juice on Dental Enamel

By

SIMON L. RUSKIN, M.D.,

ALICE T. MERRILL, PH.D.,

and

OSCAR RUSKIN, D.D.S.

NEW YORK, N. Y.

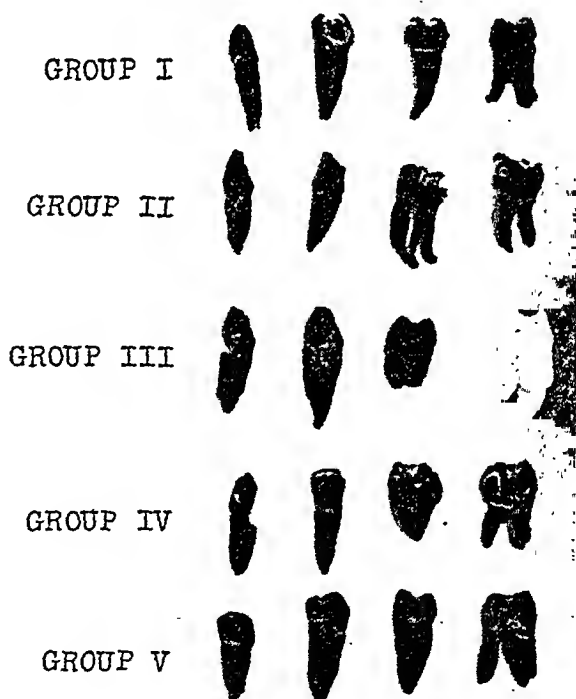
STAFNE AND LOVESTEDT, in reporting the dissolution of dental substance by lemon juice, have brought into the open an observation that has been relatively commonly observed by the dental profession, particularly in connection with advancing caries in children. Frequently the fibres of the crushed orange would be found filling the interstices between the teeth, and the caries would be observed in relationship to these deposits.

In view of the very common use of ascorbic acid for the administration of Vitamin C, an investigation was undertaken to determine whether the acid character of the vitamin was responsible for the break-down of the lime salts in the dental enamel. It is common knowledge that ascorbic acid will rapidly dissolve calcium carbonate producing calcium ascorbate. The rapidity with which ascorbic acid does this would appear to be far too rapid for an organic acid with a sugar structure. Its capacity to attack calcium carbonate resembles that of a strong inorganic acid.

In a comparative study of the chemical properties of calcium ascorbate with calcium gluconate, the remarkable ionizing properties of the ascorbate radical was pointed out. The intimate affinity of ascorbic acid to calcium was also described in the article by Ruskin on "The Parallel Action of Vitamin C and Calcium." This capacity for ascorbic acid to make calcium salts soluble, is not a haphazard one, and underlies the fundamental mobilization of calcium in the body. The theory has been proposed that ascorbic acid is the normal vehicle for serum calcium in the body, and that the break-down of a complex of calcium protein ascorbate was responsible for the fractions of ionized and non ionized serum calcium. This theory was also favorably commented on by Bourne.

An experimental investigation was undertaken to determine whether the sodium and calcium salts of

ascorbic acid would be free from the enamel attacking action. For this purpose five groups of teeth were utilized. In each group one tooth containing a beginning cavitation was used. They were placed in beakers containing the following solutions:



Group I, 10% solution of ascorbic acid, Group II, 10% solution of sodium ascorbate, Group III, 10% solution of Calcium ascorbate, Group IV, fresh orange juice, Group V, water. The solutions were changed daily and the teeth were kept immersed for one week.

In Group I, exposed to the ascorbic acid, virtually the whole enamel showed a thick layer of disintegrating substance. Where the small cavitation existed, the area became greatly enlarged. Root areas were not attacked, but did show a yellowish discoloration.

Group II, exposed to sodium ascorbate, showed no enamel disturbance nor did the cavitation show any increased size. There was no deposit around the edge of the cavitation. The tooth roots, however, showed a yellowish color somewhat deeper than the ascorbic acid, but there was no color change of the crown.

Group III, exposed to the calcium ascorbate, showed no enamel dissolution but rather a deposition of the calcium ascorbate on the surface of the whole tooth covering the root as well as the crown. The area of the cavitation also showed deposition of calcium around the edges and in the cavity tending to fill the cavity itself. This tendency for calcium ascorbate to deposit on the teeth resembled a great deal the normal calcium salts deposition commonly found in the so-called "tartar" of teeth. It would appear that it is possible to increase the calcium deposition around a tooth cavity with calcium ascorbate, thus diminishing the actual size of the cavity. This angle can be a fruitful source for future investigation in the handling of dental caries.

Group IV, The teeth exposed to orange juice showed little or no evidence of enamel dissolution over intact surfaces, in fact less than would be expected from Stafne and Lovstedt's report. However, where the cavitation of the tooth occurred, one could see a rim of enamel dissolution around the border of the cavity indicating that the exposed enamel, wherever a carious invasion had already occurred, was particularly vulnerable to the attacking orange juice. The tooth roots showed but little yellowish color change. There was no evidence of the kind of roughness of the enamel or

the general dissolution that was seen with ascorbic acid.

While it is true that the concentration of ascorbic acid employed was much greater than the ascorbic acid in the orange juice, we considered the comparison a fair one since the ascorbic acid tablets that are prescribed are taken in the solid form and when the fragments are dissolved around the teeth in the secretions in the mouth, a rather concentrated local solution occurs.

In Stafne and Lovstedt's report where the lemon juice was used over a long period of time, the enamel defects may be attributed not only to the attacking properties of the lemon juice, but also to the systemic decalcifying effect of large amounts of citrates, malates, and tartrates ingested along with the fruit juices. The effect of the orange juice on the teeth was far less destructive than that of the ascorbic acid. When, however, these were compared with the effect of sodium ascorbate and calcium ascorbate, the difference was dramatic. The sodium ascorbate failed to show any evidence of attacking the dental enamel and the calcium ascorbate far from attacking the enamel seemed to lay down a layer of protective calcium which could perhaps be studied further as an important therapeutic agent for the control of dental caries. Where Vitamin C is indicated, the sodium ascorbate or calcium ascorbate could be used with much greater safety than ascorbic acid.

Group V. The teeth exposed to water, which we used as a control showed no change.

It appeared from these experiments that the normal drinking of orange juice would not influence the enamel of the teeth except where cavitation has already been produced. Under these circumstances it would appear to be extremely important that all dental cavitation should be promptly filled, particularly in children. The use of ascorbic acid should also be replaced by a neutral salt, such as the sodium or calcium, both of which fail to show any involvement of the dental enamel.

* Part of this research was done under grant from the Physiological Chemicals Co., who also supplied the Sodium Ascorbate (Natri-C).

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Metabolism and Nutritive Importance of Tryptophane *

By

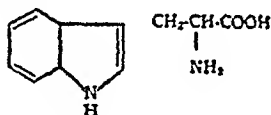
MELVILLE SAHYUN, PH.D.**

SANTA BARBARA, CALIF.

dl-TRYPTOPHANE

(beta-3-indole-alpha-amino-propionic-acid)

Structural Formula:

Empirical Formula: $C_{11}H_{12}O_2N_2$ C equals 64.9%; H equals 5.92%; O equals 15.67%;
N equals 13.72%

Properties: Tryptophane crystallizes in thin, shining rhombic and six-sided plates. It is almost tasteless. It is insoluble in cold water and in cold and hot absolute alcohol but soluble in hot water and hot 70-80 per cent alcohol and in hot pyridine. Tryptophane does not have a sharp melting point. The solubility of tryptophane is greatly enhanced in aqueous solution in the presence of other amino acids. Its melting point depends on the rapidity of heating. On heating it discolors at about 220° C., browns at 220-240° C., and melts with decomposition at 252° C.

Occurrence. Tryptophane does not occur free in nature nor does it occur in large concentration in proteins. Its concentration in most animal proteins varies from 0.5 to 2.5 per cent. It is absent in gelatin, elastin and in a number of vegetable proteins.

The tryptophane of proteins is destroyed on acid hydrolysis, racemized on alkaline hydrolysis, and can be isolated in its natural state either in a pure form or as a peptide by proteolytic digestion.

Stability. Pure dl-tryptophane is stable in acidified and alkaline aqueous solutions. Even on autoclaving for 10 to 16 hours at 15 pounds pressure in 1 N sulfuric or hydrochloric acid, tryptophane remains unchanged. However, in hot acidified solution containing traces of reducing substances such as aldehyde or keto carbohydrates (lactose, dextrose, fructose, pyruvic acid) or any of the amino acids cystine, cysteine, threonine or serine, the identity of tryptophane is either completely or partially destroyed*.

Historical: In 1838 Mulder, the famous Dutch chemist, used the term "protein" to designate an important

group of complex organic compounds known as "the quaternary azotized substances." Certain amino acids, such as cystine, glycine, and leucine, had been discovered, but no practical significance was attached to them nor were they considered to have any connection with the all-important proteins that were to become the focus of interest among leading scientists of the nineteenth century.

In 1839, Boussingault, an ingenious French agricultural chemist, put on record the first report on nitrogen balance studies made on a lactating cow. As a result of his studies, he concluded that the food of animals must necessarily contain nitrogen and, furthermore, that an adult animal, upon receiving its daily allowance of food, voids a quantity of azotized matter in its various excretions precisely equal to the quantity it receives.

Thus the door of the protein nutrition laboratory was unlocked and numerous discoveries in this important field were made. In the nineteenth century, amino acids were not considered of nutritional importance but were merely interesting substances that fascinated a certain group of curious scientists.

Some 76 years passed before tryptophane was discovered, isolated in a pure form, and subsequently synthesized. Even then its importance was not realized.

Following the discovery of tryptophane in 1901 by Hopkins and Cole, Willcock and Hopkins in 1906 showed that the protein *zein* (protein of corn), which is lacking in tryptophane, had no power to maintain growth in the young animal. This observation was confirmed by other scientists, but it was Osborne and Mendel who demonstrated effectively the indispensable nature of tryptophane. At that time two methods were used for determining the dispensability or indispensability of an amino acid. One consisted of selecting a pure protein devoid of certain amino acids and using this protein as the only source of nitrogen in the diet of the experimental animal. (Vitamins were not known then). The other consisted of employing hydrolyzed proteins from which one or more amino acids had been removed to the best technic then available.

INDISPENSABLE NATURE OF TRYPTOPHANE

Tryptophane is the only naturally-occurring amino acid that possesses an indole ring in its chemical structure, and it is believed that by this virtue the animal system cannot synthesize this protein constituent; hence its indispensability (1). All experimental ani-

* This paper was supported in part, by a grant from the Dow Chemical Company, Midland, Michigan.

** Present address: 265 La Arcada, Santa Barbara, California.

Submitted January 24, 1948.

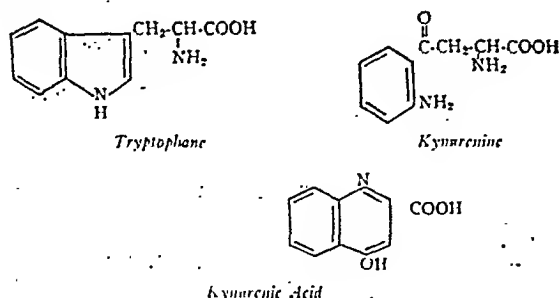
* Sahyun, Melville, Stanford Med. Bull. 6, 303, 1948.

mals, including mice, rats, dogs, chickens, etc., and man, kept on diets deficient in this amino acid, go into negative nitrogen balance (1-4). In rats there is first negative nitrogen balance, followed by loss of appetite and loss of weight. (These symptoms are characteristic of all experimental diets deficient in any of the essential amino acids). Should the rat be kept on a tryptophane-deficient diet, a reduction of blood albumin and globulin occurs and cataracts develop (5, 6). These symptoms and acute lesions can be prevented by the addition of tryptophane to the diet; however, if the deficient diet is continued, the animal continues to lose weight and finally dies. The cataracts observed in animals kept on tryptophane-free diets are, according to Albanese and Buschke (5), very similar to those observed following riboflavin deficiency. According to Berg and Rose (7), the intake of tryptophane is most nutritional and effective when given mixed with diets.

TRYPTOPHANE METABOLISM

Little is known of the intermediary metabolism of tryptophane. The early work of Berg and Potgieter (8) and of du Vigneaud, Sealock and Van Etten (9) indicated that good nutrition in the rat can be maintained equally well by both the racemic *d*- and the natural *l*-tryptophane. This suggests that both forms of tryptophane are susceptible to transamination. Recent research in this field tends to show that *l*-tryptophane causes the excretion of kynurenic acid whereas *d*-tryptophane is excreted unchanged. Albanese and Frankston (10) have recently reported that the administration of *dl*-tryptophane to human beings causes the excretion of a compound that forms indigo red when treated with iodine.

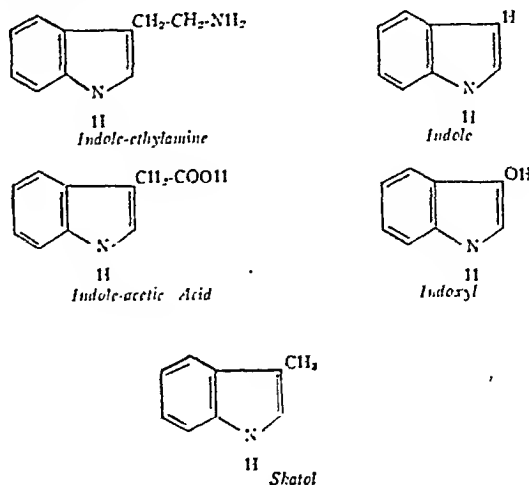
The administration of *l*-tryptophane or β -3-indolepyruvic acid gives rise in the urine of certain animals to kynurenic acid and kynurenine. Gordon, Kaufman and Jackson (11) found that rats, guinea pigs, dogs and coyotes synthesize kynurenic acid from *l*-tryptophane, whereas men and cats do not. Apparently kynurenic acid and kynurenine are intermediary products in the metabolism of tryptophane, and the presence or absence of these metabolic products in the urine varies with species differences and the inherent ability to destroy kynurenine. The chemical configuration of these substances as related to tryptophane is as follows:



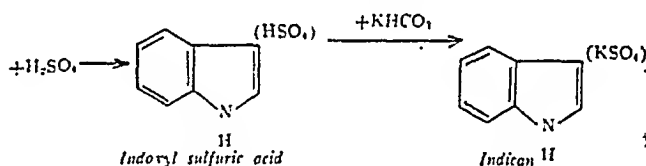
TRYPTOPHANE AND PUTREFACTION

Tryptophane undergoes putrefaction in the intestines with formation of toxic compounds. Many of

these have been known and identified as indole, skatol, indoleacetic acid, indolylacetic acid and skatolylglycuronic acid. The manner in which some of these compounds are formed is illustrated in the following structural formulas:



The breakdown of tryptophane to indole seems to occur in the bowel. Absorption of indole then takes place and the formation of indoxyl and its conjugation with sulfuric acid occurs in the liver, thus giving rise to indican.



INTERRELATIONSHIP OF TRYPTOPHANE AND

VITAMIN B₆

Lepkovsky and Nielsen (12) first reported the presence of a yellowish-green pigment in the urine of rats kept on a pyridoxine-deficient diet. This pigment was subsequently isolated and identified as xanthurenic acid (4:8-dihydroxyquinoline-2-carboxylic acid). It was found to be excreted by dogs, pigs, and mice but not by chicks (13-16) when these animals were kept on a pyridoxine-free diet that contained tryptophane or protein containing tryptophane. This intimate relationship between tryptophane and xanthurenic acid was first noted by Musajo (17) in his studies of pyridoxine-free diets of rats and rabbits. He observed that whenever these animals were kept on tryptophane-free diets xanthurenic acid disappeared from the urine and reappeared when this amino acid was again added to the diet. Ried, Lepkovsky, Bonner and Tatum (18) showed that only *l*-tryptophane and kynurenine were capable of producing xanthurenic acid in the pyridoxine-free diet. Indole-3-pyruvic acid (19, 20), *d*+ tryptophane (9, 21), indole-3-lactic acid (22) and abrine (methyl-tryptophane) (23-25) did not contribute any xanthurenic acid in the vitamin B₆ deficient diet. Since pure xanthurenic acid fed to pyridoxine-deficient animals is excreted unchanged, this indicates that their metabolism must follow a different path from that of *l*-tryptophane. It is noteworthy

that the feeding of tryptophane or proteins such as casein to B_6 -deficient animals not only increases the excretion of xanthurenic acid but aggravates the ill health of these animals. It therefore appears that protein metabolism (and that of tryptophane in particular) is intimately related to pyridoxine. Schweigert and co-workers (26) showed in pyridoxine-free diets that the pyridoxine content of these animals decreases with an increase in the protein content of the diet; furthermore that fatty livers develop. Axelrod, Morgan and Lepkovsky (27) reported that the ingestion of tryptophane by dogs fed pyridoxine-free diets produced nausea, anorexia and sometimes collapse. These symptoms were not observed after the ingestion of tryptophane when only moderately severe B_6 deficiency was induced. Other syndromes, such as dermatitis, were noted in pyridoxine-deficient rats kept on a high protein diet (28). Sarma, Snell and Elvehjem (29) observed that indole or *dl*-tryptophane caused retardation of growth in rats kept on diets low in pyridoxine or pyridoxal.

One may safely conclude that for the proper metabolism of this important amino acid, tryptophane, vitamin B_6 must be adequately provided in the diet of animals. Little is known as yet about this interrelationship in man.

TRYPTOPHANE AND NIACIN

The urinary excretion of nicotinic acid by dogs has been shown to be related to the amount of protein ingested in the diet. Wintrobe et al. (30) were unable to produce niacin deficiency in swine kept on diets containing 26 per cent protein, but a deficiency developed when the protein content of the experimental animal was reduced to a level of 10 per cent. On low

protein diets niacin deficiency could be prevented by adding niacin to the diet. On adequate protein intake the white rat is ordinarily capable of synthesizing this vitamin; however, its growth is retarded when either corn meal or corn grits (31) is added to its protein-low diet. In investigating the cause of this unusual syndrome, Krehl, Teply, Sarma and Elvehjem (32) found that a tryptophane deficiency or tryptophane-deficient protein was the causative factor; thus these investigators showed that the addition of as little as 0.05 per cent of *l*-tryptophane to such low protein, niacin-deficient diets would correct the deficiency. Nutritionally, 50 mg. of *l*-tryptophane was the equivalent of 1.0 to 1.5 mg. of niacin. Further research has clearly indicated that the beneficial effect of high protein diets in niacin deficiency is related to its tryptophane content. Rosen, Huff and Perlzweig (33) demonstrated conclusively that the urinary excretion of nicotinic acid is increased with increased tryptophane intake and decreased with either decreased intake of tryptophane or protein containing tryptophane.

The deleterious effect of corn grits which has been observed in animals normally requiring niacin is believed to be due to another factor besides tryptophane deficiency. Woolley (34) investigated this problem and claimed to have isolated a "pellagragenic" substance from corn by chloroform extraction which he noted was capable of simulating niacin deficiency. He also claimed that 3-acetylpyridine, an analog of niacin, is also capable of producing pellagra-like syndromes in the experimental animal.

In summation, there seems to be good evidence that *l*-tryptophane is the precursor of niacin synthesis in the experimental animal, although the intermediate steps of synthesis are still obscure.

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Nutrition Notes

Dietetic Service in English Hospitals *

Owing to the fact that English hospitals have evolved from charitable institutions for the very poor (the wealthy being taken care of in Nursing Homes), it is not surprising that many ideas, deeply rooted in tradition have so long survived. In earlier times the provision of food for patients was a decidedly secondary consideration. Parsimony in the kitchen was considered commendable and only one "square" meal a day could be expected. Furthermore, there still remains a confused inter-relationship between nursing and catering, inasmuch as formerly all food was prepared by nurses. As recently as 1942, cases were described in which the nutritive value of the food was seriously defective, especially in protein, vitamins and calories. The solution of this serious problem is yielding to a division of labor between caterers and nurses, the latter taking charge of the food once it reaches the wards. The British Medical profession of course is fully aware of the immeasurable importance of nutrition in hospital populations and more money is now being spent to improve it.

In the pre-Listerian era there was scarcely a person in hospitals who was not "swinging a high temperature in the evenings" and hospitals got into the habit of not providing cooked substantial suppers for these patients as the average person did not require it, owing to his condition. However, in tuberculosis hospitals and sanatoria, for at least fifty years, the diet has been adequate and attractive. The physician himself must be the judge of what kinds of diet are required, so that caterer, dietitian and nurse must take their cues from him at all times.

International Agricultural Collaboration

For the past six years a fairly intensive cooperative agricultural program has been carried out by the U. S. Government with other American Republics, focused on development of crops which are complementary to the United States economy. With the passage of Public Law 402 by the U. S. Congress in January 1948, this cooperative work is being extended into countries of the Eastern Hemisphere. One reason for this far sighted movement is the fact that trees and plants producing certain drugs and insecticides are not indigenous to this country and cannot be grown here. Cinchona is a case in point, and quinine remains the sheet anchor of anti-malarial therapy. Pyrethrum, a valuable insecticide is obtained from a herbaceous perennial, *Chrysanthemum cinerariaefolium*, a native of Yugoslavia, but grown now chiefly in East Africa and Japan. Rotenone, a derivative of *derris* and *lonchocarpus* will be obtainable in the Western Hemisphere from now on, owing to cooperative efforts of

our Department of State with Puerto Rico, Brazil, Ecuador and Peru.

Because of world food shortages, greater emphasis than ever before has been placed on the need for high per-acre food production in the Western Hemisphere. An important feature of the U. S. program of international collaboration in agriculture has consisted of steps taken to improve health conditions in certain tropical American areas where complementary crop research and experimentation is being conducted (see The Record, Vol. IV, No. 5, issued by the Dept. of State, Washington, for a complete resume of cooperative efforts, particularly with respect to the control of Tropical Diseases).

Folic Acid

It has now become general knowledge that while folic acid produces good blood remissions in pernicious anemia, it does not protect the spinal cord and peripheral nerves from the degenerative effects, so commonly accompanying this disease. During a hematological remission induced by folic acid, even with the hemoglobin value and red blood cell count at a supernormal level, the subacute combined degeneration of the cord may begin and progress unhindered. For that reason, physicians who employ folic acid in Addisonian anemia usually protect the nervous tissues by liver injections, 15 units of refined extract, from two to four times per month. There is evidence also, as revealed by the work of Wilkinson (1), that the smear picture of the blood even in remissions produced by folic acid seldom shows a complete return to a pure normocytic morphology, but usually considerable persisting macrocytosis. It is true, then, that folic acid does not possess an "anti-subacute-combined degeneration" factor and, by contrast, it appears probable that liver extract does contain such a factor, though it cannot be decided whether the favorable effect of liver extract on cord changes is due to a special and specific fraction of the extract or to a side effect of the same element which initiates and brings to maturity the remission blood changes.

Wilkinson shows, as have others, that folic acid produces good hematological effects only in macrocytic anemias with some degree of megaloblastic bone-marrow change, and that it has no effect on normoblastic marrows. There is a response to folic acid in pernicious anemia, the so-called "pernicious anemia of pregnancy" and the macrocytic, megaloblastic anemias of infancy, pellagra, sprue, steatorrhea, and celiac disease, as well as nutritional macrocytic anemias (e. g. jungle anemia) and possibly in many cases of achrestic anemia. Responses are irregular in steatorrhea and liver extract may be required to produce complete remissions. Folic acid has no beneficial effects on hypochromic microcytic anemias, hemolytic anemias, refractory megalocytic anemias with normoblastic mar-

* Discussion on the dietetic service of the hospitals of the future. Proc. Roy. Soc. Med., Vol. XLI, No. 4, 209-216, April, 1948.



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rows, acute and chronic leukemias of all types, leucocythroblastic anemia, chronic ulcerative colitis, anemias secondary to myxedema or hyperthyroidism, toxic or idiopathic aplastic and hypoplastic anemias, agranulocytosis, neutropenias, and thrombocytopenic purpura, but it does relieve leucopenia and thrombocytopenia when these are features of a nutritional deficiency or a megaloblastic anemia. It would seem that "shot-gun" treatment with mixtures of folic acid, iron and liver extract are not to be recommended unless one has a very clear idea of what he may expect from each ingredient in the dose-level employed.

It is to be noted, as pointed out by Davidson et al. (2) that many cases of megaloblastic anemia of pregnancy fail to respond to liver extracts but do respond to folic acid. The three pteroylglutamates are designated vitamin B₉, B₉ conjugate and the fermentation factor. Usually the term *Folic Acid* refers to vitamin B₉ or pteroylglutamic acid (P. G. A.). All three, however, are hematologically active in man. Whether man normally requires this vitamin is not known definitely. It is active in correcting the defects of both the hematopoietic and gastrointestinal symptoms in sprue (3). Just how a deficiency of pteroylglutamates develops in man is not clear. Confusion in terminology still perplexes the practitioner. Pteroylglutamic acid (P. G. A.) the agent usually employed clinically and customarily called Folic Acid has also been known under the following names — vitamin M, factor U, norite eluate factor, vitamin B₉ and *Lactobacillus casei* factor. Increasing knowledge of folic acid and the enzyme systems associated with it promises to create a vital chapter in our knowledge of nutrition.

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Breakfast in West Virginia

For decades the "continental" breakfast has been a cup of coffee and a cigarette while not infrequently there is a tendency to omit the coffee. The motivation to matitudinal starvation was never any single idea. The intention to reduce and a certain conception of "smartness" as well as the influence of custom were important, although sometimes a person who was a gourmet at dinner had a constitutional inability to face an adequate first meal. The *petite dejeuner*, continentally speaking, is seldom more than a concession to custom.

In America (these United States particularly) coffee is customarily associated with a doughnut or sweet cake, all of which is partaken of in a rush because of the urgency and call of the busy day. It is unlikely that anyone in this country requires more than ten minutes to devour his or her breakfast. Wheat cakes will be eaten by those who are manually employed.

Millions do not even think of breaking fast until noon.

The question arises as to whether the total or partial eclipse of breakfast has had any influence on the health, vitality and efficiency of Americans.

The State of WEST VIRGINIA has put its official seal on an answer in the affirmative, and during the past year, if you live in this beautiful state, you probably have become breakfast conscious. "Start the day the good breakfast way" is a slogan employed by the West Virginia State Nutrition Committee under the able presidency of M. Estelle Ingoldsby, R. N., and the ramifications of this Committee's work are many and far reaching. A careful survey by a fact-finding group in 1944 of the children in three counties (1207 children from the fifth grade through the 10th grade) was detailed enough to make complete dietary histories, which at once revealed poor breakfasts as a state-wide problem of considerable gravity. Out of every 100 children, 14 ate no breakfast at all. Of the 86 who ate some kind of breakfast, only 10 per cent were good. By "good" is meant the use of fruit, milk and cereal.

Special projects of this Committee also include nutrition education through labor organizations, state legislation of the enactment of white flour and bread, and the *teaching of nutrition in elementary schools*. Nine key cities were selected for intensive, better-breakfast campaigns, utilizing the press, radio, and even free specimen breakfasts at down-town cafes. A "good breakfast week" was proclaimed by the Governor. Health Commissioner N. H. Dier, M.D., gave the movement his unqualified support. Even groceries in their newspaper advertisements captioned their displays with such slogans as "a rousing Breakfast." The State Supervisor of Elementary Schools has observed already among school children "better learning attitudes; more alertness through the course of a morning's work; and general health improvement."

West Virginia is to be commended most highly for its signal efforts in training a new generation to understand the folly of the continental breakfast. In this state it will soon be quite reprehensible to "skip or skimp" at the opening meal of the day. The fellow who sits up at a counter blowing cigarette smoke over a cup of coffee probably has already become *persona non grata* in West Virginia.

Every State in the Union ought to do what West Virginia is doing and has done. Where it appears difficult to discover an *entre* into the vast problems of nutrition confronting us, it is a most practical step to focus on a single meal, particularly the day's first meal. The inference is that frequently all meals are as "bad" as breakfast, but education covering the early morning hours is likely to influence the whole day. The beautiful 160 page report on this campaign, can probably be obtained by writing directly to the West Virginia State Nutrition Committee, State House, Charleston, W. Va.

Abstracts on Nutrition

JOLLIFE, N. AND FEIN, H. D.: *Some observations on acute and chronic glossitis.* (Rev. Gastroent., Feb. 1948, V. 15, No. 2, 132-145).

Deficiencies of niacinamide and of folic acid may each lead to an acute glossitis as the only objective clinical manifestation of these deficiencies. The chronic glossitis of malnutrition sometimes responds to niacinamide alone, but other nutritional deficiencies also may cause a similar chronic glossitis. The "atrophic" tongue is considered to be the end stage of a long series of changes, which frequently were initiated by a generalized papillary hypertrophy, although an atrophic tongue may develop with extreme rapidity in pneumonia.

MONTUSCHI, E. AND MELTON, G.: *Severe diabetic neuropathy with right phrenic palsy.* (Proc. Roy. Soc. Med., Feb. 1948, V. XLI, No. 2, p. 101).

A very severe diabetic male aged 57 did well on insulin and diet, but developed diabetic retinitis in the right eye, wasting of shoulder-girdle muscles on the right side, severe wasting of muscles of both legs and bilateral foot drop. Gradually he improved considerably, but showed poor air entry and diminished respiratory excursion at the right base. X-ray films showed paralysis of the right dome of the diaphragm. It is pointed out that a marked polyradiculitis with raised protein in the cerebro-spinal fluid and an Argyll-Robertson pupil are not common in diabetes. The *phrenic palsy has not been previously described in diabetes*, but it was apparently due to diabetes.

FRAZER, A. C.: *Etiology of steatorrhea.* (Brit. Med. Jour., Oct. 25, 1947, 641-645)

This is a lucid, physiological description of the digestion, absorption and distribution of fat in the human subject. It is possible that a defect in phosphorylation may be an etiological factor in sprue, but direct evidence of this is lacking. A normal person on a diet containing 50 grams of fat absorbs 95 per cent or more of the ingested fat.

BLACK, D. A. K. AND FOURMAN, L. P. R.: *Some problems of tropical sprue.* (Brit. Med. Jour., Oct. 25, 1947, 645-647).

The authors have found that yeast extract in large doses has a favorable effect on fat absorption. Clinical benefit from yeast treatment in patients with chronic sprue has been seen in the U. S. A. and it is more convenient than injections of crude liver extract. A number of patients with sprue become acutely ill, with salt-deficiency, dehydration and watery diarrhea. The diarrhea must be controlled with a sulphonamid and parental liver, and moderate amounts of NaCl supplement added to the diet.

OLSEN, T.: *Periarticular calcifications in hypercalcemia.* (Nordisk Med., Oct. 10, 1947, V. 36, No. 41, 2047-2049).

The authors describe two cases of periarticular and para-articular calcifications about the knee and finger joints in middle-aged women. They had tetany due to removal of the parathyroids and were receiving A. T. 10 and vitamin D₂.

PALMER, L. J.: *Diabetes mellitus (errors in diagnosis).* (Bull. Mason Clin., Sept. 1947, V. 1, No. 3, 98-101).

The author believes that although non-diabetic glycosuria is frequently recognized as such, more frequently there is a failure to make a diagnosis of diabetes mellitus early in the course of the disease. Blood sugar estimations following meals and sugar tolerance tests provide the means of differentiating the two conditions. He describes the case of a woman of 45 with renal glycosuria who had been treated erroneously for diabetes by means of diet and insulin for 12 years. Interestingly, her daughter who also had renal glycosuria was likewise treated in error for diabetes. Both suffered distressing insulin reactions.

CUMINGS, J. N.: *Nicotinamide and blood sugar.* (Brit. Med. Jour., Oct. 18, 1947, 613).

Clinical experiments showed that, in general, nicotinamide is without effect on the blood-sugar levels in normal subjects or in diabetic patients. The absence of any effect on the blood co-enzyme content is possibly further proof of this fact.

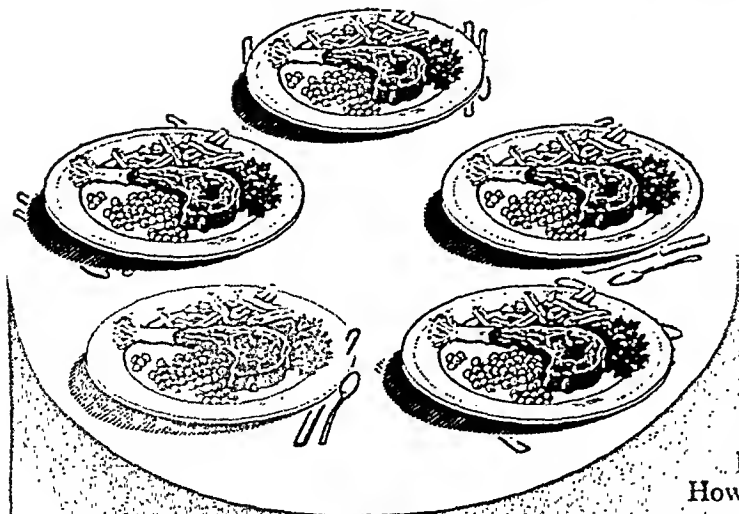
BIRMINGHAM, J. R.: *Congenital pitressin resistant diabetes insipidus.* (Alex. Blain Hosp. Bull., Feb. 1948, V. 7, No. 1, 19-26).

A case report is made of an infant in whom recurrent bouts of unexplained fever were found to be due to dehydration from extreme polyuria. The polyuria was not due to neurohypophyseal deficiency since it did not respond to pitressin, and since the urine contained an anti-diuretic substance of pituitary origin, the excessive diuresis was probably due to a specific abnormality of function on the part of the renal tubules preventing the excretory mechanism from responding to the post-pituitary antidiuretic hormone.

FOURMAN, L. P. R. AND SPRAY, G. H.: *Absorption of vitamin D in steatorrhea.* (Brit. Med. J., Jan. 24, 1948, 142-144).

A case of osteomalacia secondary to steatorrhea is described. The bone disease progressed despite treatment with a low fat diet and vitamin D and calcium supplements. On a daily intake of 70 gms. of fat, 4.6 grams of calcium, and 12,000 i. u. of vitamin D orally, the patient retained only 1.9 grams of calcium

*only 21 per cent of persons consuming
average diets
obtain protective
quantities of
vitamins.**



Were this serious indictment of four out of five menus based on supposition it might well be questioned.

However, it is not conjecture, but has been arrived at by analysis of recorded diets of 3336 persons as well as by actual chemical assay of the dietaries of 71 persons. In summing up the study the authors state: "Any conclusions as to the deficiencies present, when drawn from the analysis of the food of the test group, may be regarded as conservative in relation to the nation as a whole."

However, poor selection in the choice of food is only one factor contributing to this situation. The vitamin content of many foods as prepared for consumption is often considerably less than the vitamin content when first produced.

Handling of vegetables and fruits in picking, storing, packing and shipping frequently reduces vitamin content. As much as eighty per cent of ascorbic acid and ninety per cent of thiamine may be lost through overcooking or prolonged soaking.

While careful selection and preparation of vitamin-rich foods will offset some of the hidden factors operating to curtail adequate vitamin intake, the more practical physician will wish to supplement those diets which possibly may be faulty.

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*Lockhart, E. E.; Harris, R. S.; Tapia, E. W.; Lockhart, H. S.; Nutter, M. K.; Tiffany, V., and Nagel, A. H.: J. Diet. Assn. 20:712 (Dec.) 1944.

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in 16 days. With the same dose of vitamin given intramuscularly she retained six grams of calcium in 16 days. Apparently a failure to absorb vitamin D occurs in osteomalacia due to steatorrhea.

SCHWARTZ, S. O. AND ARMSTRONG, B. E.: *Treatment of iron deficiency (hypochromic anemia)*, (Miss. Valley Med. J., January 1948, V. 70, No. 1, 2-13).

Of the 55 cases of anemia studied, almost all (52) had become anemic as the result of long continued menorrhagia. The authors attempted to make an evaluation of the following points — (a) Adequacy of the iron dosage, (b) Relative value of different iron salts, (c) The supplemental value of liver and stomach extract, vitamin B complex and copper, (d) The length of time therapy should be continued. The therapeutically induced recovery period is divisible into three phases: (a) A rapid regenerative phase lasting about two months, (b) A therapeutic "overshoot" occurring in the third month, (c) A return to the individual's normal level between the fourth and sixth months. 250 mgm. of iron per day produced as good results as larger doses ranging up to 439 mgm. per day. No difference in response could be shown between the ferric and ferrous salts of iron. The addition of copper to a suboptimal dose of 100 mgm. of ferric iron per day failed to produce an optimal response. The addition of vitamins of the B complex, copper, liver and stomach extracts did not enhance the action of iron, even in the low income group. In the iron deficient patient, iron therapy must be continued for at least three months for maximum responses and replacement of depleted stores.

MINOT, GEORGE R.: *Nutrition and health*. (Nutrition Reviews, Nov. 1947, V. 5, No. 11, 321-322).

Dr. Minot indulges in a number of wise sayings gleaned from years of experience . . . the happiness of a people go hand in hand with plenty of good food . . . the most fertile field in the world of medical research today is nutrition . . . we must learn more about the enzymes in food . . . it is difficult to obtain an adequate dietary history . . . a proper diet of natural foods is all that is necessary for prevention of most diseases caused by faulty nutrition . . . what is optimal nutrition? . . . poor quality proteins are more harmful than a diet low in protein . . . we must learn how to diagnose subclinical deficiencies in human beings . . . dental caries is the most widespread nutritional defect . . . the essential trace elements, such as cobalt and zinc, stand as a challenge to physiologists and nutritionists . . . more vitamins may possibly be identified.

HYDE, L. AND HYDE, B.: *Toxicity of large doses of vitamin D (Ertran)*, (Ann. Int. Med., Oct. 1947, V. 27, No. 4, 617-627).

The authors show that large doses of vitamin D

taken over a period of time may be toxic and can cause metastatic calcification, renal failure and death. The case reported is a 59 year old white male who received 200,000 units of vitamin D (Ertran) daily for 17 months. He noted the development of hard subcutaneous nodules of both arms after 10 months of this treatment. X-ray showed extensive subcutaneous calcification throughout the body. Renal insufficiency was present. Treatment, which consisted in a low calcium diet and cessation of vitamin D, resulted in a reduction of subcutaneous periarticular calcification and symptomatic improvement. Concentrated vitamin D medication may prove toxic — in any case, its value in rheumatoid arthritis is doubtful.

HAMIL, B. M., MUNKS, B., MOYER, E. Z., KAUCHER, M. AND WILLIAMS, H. H.: *Vitamin C in the blood and urine of the newborn and in the cord and maternal blood*. (Am. J. Dis. Child., Oct. 1947, V. 74, No. 4, 417-433).

The vitamin C was determined in blood from the umbilical cord, in venous blood of the mother and in the capillary blood and urine of infants during their first week of life. Considerable variation in the level of vitamin C in the blood among individual women and infants was found. Concentrations of the vitamin in urine were high during the first two days of life but dropped to low levels by the fourth day. The declining levels of vitamin C in urine and plasma during the first week of life suggest that the physiological processes of intra-uterine life require greater tissue saturation of the vitamin than is needed in the gaseous environment of extra-uterine existence.

BOCK, J.: *Serum protein fractions of normal old people*. (Nordisk. Med., April 16, 1948, V. 38, No. 16, 792-797).

There is a decrease of total serum protein concentrations in normal old persons. Bock showed that in females younger than 80 years, the serum protein concentration was 6.64 ± 0.39 per cent and for females between 80 and 95 years 6.24 ± 0.37 per cent. For younger males the values were 6.63 ± 0.30 per cent and for the older group 6.33 ± 0.28 per cent. These changes are due to a fall in the albumin fraction. A slight increase in the globulin fraction was found which of course does not compensate for the decrease of the albumin. The relative albumin per cent decreases to a significant extent with advancing years. For younger females the value was 65.9 ± 6.18 per cent and for the older ones 60.0 ± 5.9 per cent. For the younger males the value was 63.6 ± 5.32 per cent and for the older 58.6 ± 5.49 per cent. It is uncertain whether these changes are due to failure of appetite with decreased protein intake, or to a decreased capacity in the protein forming organs.

Editorial

HOW CAN WE IMPROVE OUR MANAGEMENT OF PEPTIC ULCER?

LIKE THE POOR, the problem of peptic ulcer is always with us. Whenever a large series of cases is followed up for a period of 10 years, we can find, on the whole, very little to be proud of, because of recurrences and fatal complications. The insurance companies have noted that a remarkable percentage of cases, once diagnosed as peptic ulcer, ultimately die of cardiac disease. We have learned that massive hemorrhage is more often fatal than we had hitherto felt. Perforation still kills too many persons usually owing to delay in surgical intervention. Subtotal gastrectomy has won for itself a unique position in the cure of ulcer, but it should be remembered that the operative mortality, except in the hands of experts, remains forbiddingly high. It seems probable that more cases ought to be treated surgically early in the course of the disease, yet there is an understandable tendency on the part of the internist as well as the surgeon himself to postpone surgical intervention so long as the patient appears to be doing well on medical treatment.

In medical treatment, many authorities agree that the one measure of outstanding importance is *rest*, especially mental rest and freedom from anxiety. Certainly diet, alkalis, and belladonna continue to contribute important elements and ought not to be neglected. Psychosomatic medicine has evolved a "profile" for these patients which contains, in varying proportions such elements as dependency, frustration and a tendency to persist in a course of action under circumstances highly unpropitious to their object.

There are many reports which now make it increasingly probable that emotional disturbances, especially those which arise from frustrations at a very deep level of consciousness, play a vital role in the continuance of ulcer, if not in its genesis.

People worry about every conceivable kind of thing, and often the cause of worry seems surprisingly insignificant when discovered. But the resolution of even quite superficial anxieties may make immediate improvement in the course of the disease.

From a practical standpoint there are four points of importance to be observed if we are to improve our record in the management of ulcer. First, the diagnosis is not easy even for the exclusive roentgenologist, and difficult for the amateur; but by taking more time and greater pains and by repeated fluoroscopies the percentage of correct diagnoses may be increased. Second, there are some patients who cannot be controlled even in the matter of rest, diet and medicine, and they should either be brought under control or warned as to what the future may hold. Third, the physician should take time through conversation, superficial analysis and sympathetic study to determine the emotional status of the patient in an attempt to remove at least his superficial anxieties or, if this is impossible, refer the patient to a competent psychiatrist. Fourth, in the obdurate case of long-standing, especially with a history of hemorrhages, the patient should be treated by radical surgery without too much delay.

Book Reviews

CRYSTALLINE ENZYMES. By John H. Northrop, Moses Kunitz and Roger M. Herriot, pp. 351, Columbia University Press, New York, 1948, \$7.50 (2nd Edit.).

A fascinating treatise, highly specialized but provocative and useful. The first edition appeared in 1939. At present, some 35 enzymes have been obtained as crystalline proteins and the identity of the enzyme and the crystalline protein has been widely accepted. Now, three hitherto apparently independent problems — the formation of proteins, of enzymes and of viruses which are of the first importance for the comprehension of the mechanics of living matter, have been reduced to a single problem, viz., the mechanism of the synthesis of proteins in general. Two new enzymes, ribonuclease and hexokinase are described. Other sub-

jects dealt with include the solubility method for determining the purity of proteins, protein synthesis and virus formation and the isolation of crystalline diphtheria antitoxin. The work has emerged from the Rockefeller Institute for Medical Research and should be read by all gastroenterologists.

SYNOPSIS OF PEDIATRICS. By John Zahorsky, M.D., pp. 449, The C. V. Mosby Co., St. Louis, 1948, \$5.50.

This is the fifth edition of this work. It is a compact, practical and profusely illustrated treatise. The author has included advances from the standpoint of the social sciences and is at great pains to describe the uses of the newer drugs. The book is highly recommended as a worthy member of the "synopsis" series.

General Abstracts Of Current Literature

ABSTRACT EDITOR — M. H. F. FRIEDMAN

Jefferson Medical College

1025 Walnut Street

Philadelphia, Pennsylvania

CLINICAL MEDICINE

MOUTH AND ESOPHAGUS

TANNER, N. C.: *The present position of carcinoma of the esophagus.* (Post-grad. Med. J. V. 23, p. 109, 1947).

This paper, illustrated by 26 figures, is too long for a concise review. It is an excellent summary of the present status of surgery for esophageal cancer. Successful resections are now being carried out, often with restoration of deglutition. Mortality however, is still high. The major obstacle to be overcome is that of diagnosis made too late for resection. Several operative procedures are available and the choice of a particular procedure is determined by the extent of the malignancy and the condition of the patient. Best results are achieved by the combined efforts of the radiologist, esophagoscopist and surgeon in arriving at the diagnosis and the surgical treatment.

PERONNE, J. A., FLEMING, W. H. AND WHITAKER, T. R.: *Congenital atresia of esophagus with tracheoesophageal fistula: report of six cases.* (Arch. Otolaryngol., V. 46, p. 668, Nov. 1947).

Death from congenital atresia of the esophagus is inevitable and results usually from starvation or aspiration pneumonia. In six infants studied by Peronne et al. excessive amounts of mucus in the mouth and throat were found. Iodized oil rather than barium sulfate should be used for diagnostic roentgenograms since the former is much safer and gives rise to fewer complications than the barium if it is aspirated into the lungs. A tracheo-esophageal fistula, permitting gastric contents to pass from the lower esophageal segment into the trachea, was present in three infants and death in these was due to pneumonia. The regurgitation of feedings in several of the infants led to the erroneous tentative diagnosis of pyloric stenosis. The pulmonary complications may also mislead as to the primary nature of the disease.

STOMACH

GRAHAM, R. M., ULFELDER, H. AND GREEN, T. H.: *The cytologic method as an aid: the diagnosis of gastric carcinoma.* (Surg. Gynecol. and Obstet., V. 86, p. 257, March 1948).

Carcinoma of the stomach is the most frequently encountered malignant lesion today. The most recent figures of some authors give only a five to 6.5 per cent cure rate at the end of five years for this disease. Papanicolaou in 1927 introduced a cytologic method

for the diagnosis of carcinoma, which depends upon the desquamative nature of malignant growths of the uterus. In 1937 Dudgeon and Wrigley reported 66 per cent accuracy in the diagnosis of cancer of the lung through recovery and vital staining of cells in the sputum, and Wandall found malignant cells in the sputum in 86 per cent of 100 cases of pulmonary carcinoma. In the past year, gastric aspirations from fifty patients suspected of cancer of the stomach were studied by the cytologic technique at the Vincent Memorial Laboratory. The fasting residuum was aspirated, centrifuged and the sediment spread on a glass slide and fixed for 15 minutes in equal parts of ethyl ether and 95 per cent alcohol, then they were stained by the Papanicolaou method. Normal or partially degenerated epithelial cells, erythrocytes, neutrophils, lymphocytes and histiocytes as well as bacteria were seen. The malignant cells often appear in groups. The nuclei are hyperchromatic and usually contain prominent nucleoli. There are no sharp cellular borders, and the cytoplasm often shows vacuolization, a characteristic of adenocarcinoma. In this series of fifty cases, cancer cells were seen in 15. The error in the positive cases is 37.5 per cent, since 24 in the series had gastric cancer. These 24 were explored and seven had resectable lesions, five of whom had malignant cells in the gastric contents previously. One of the two failures had a scirrhous non-ulcerating carcinoma. In 26 cases in which no evidence of cancer was shown, 14 were explored. Twelve of these had benign gastric ulcers, one a neurofibroma, and one a duodenal ulcer. The error in the negative (benign) cases is 3.8 per cent. In two described cases of gastric ulcers, the cytologic method of determination of carcinoma was confirmed by pathologic sections as early carcinoma, one of which had been reported as benign until the sections were reviewed.

RUNDLES, R. W. AND BAYLIN, G. J.: *Urecho-line in the treatment of motor abnormalities in the gastrointestinal tract of neurogenic origin.* (Am. J. Med., V. 4, p. 456, March 1948).

A major complication following vagotomy has been found to be prolonged gastric retention and gastric atony and dilatation. Urecho-line (urethane of beta-methyl-choline chloride) was found to be the most effective of parasympathomimetic drugs with the least side reactions. Twenty-two patients subjected to vagotomy were treated satisfactorily. The dose of urecho-line was five milligrams hypodermically or 10 to 50 milligrams orally.

In three patients with diabetic neuropathy showing

gastric retention and disorganized gastrointestinal activity; urecholine was effective in restoring normal intestinal motility. Clinical symptoms also disappeared.

Return of normal bowel habits and absence of clinical symptoms resulted from the oral use of urecholine in three patients with megacolon treated for eight to 12 months.

PORGES, O.: *The jejunal syndrome*. (Am. J. Med., V. 3, p. 177, August 1947).

After partial resection of the stomach for peptic ulcer there may develop a disorder termed "dumping" syndrome. The patients become tired and sleepy after meals; they are nauseated, have a pressure sensation over the stomach, and perspire. Fainting and syncope may occur. This is due to severe enteritis or jejunitis and may be seen in some patients without resection of the stomach. The author advocates the term "jejunal syndrome" as more appropriate. There is an increase in the soaps in the feces and an accelerated passage of food through the small intestine. This is not seen in cases with resected stomachs who do not have enteritis. The enteritis is not connected with a vitamin deficiency and cannot be cured with vitamin medication. Severe enteritis may turn into sprue either by failure in absorption of vitamins or because of inadequate vitamin intake.

HAYES, J. D.: *Cancer of the stomach*. (J. Arkansas Med. Soc., Jan. 1948, V. XLIV, No. 8, 181-183).

Cancer of the stomach kills 40,000 persons annually in the U. S. A. Over 50 per cent of gastro-intestinal cancers occur in the stomach. The pessimism of Welch in 1885 with respect to the curability of this lesion largely remains, but earlier diagnosis, pre-operative assessment of the type and extent of the growth, as well as marked improvement in surgical technique, have given us grounds for increased optimism. Walters reports five year survivals after gastrectomy for cancer in 62 per cent of the less violently malignant lesions but only in 20 to 30 per cent of the more actively growing and infiltrating types. Boorman's four types are well to use for pre-operative classification. Epigastric distress after 40 years of age is the symptom which may lead to an early diagnosis. Psychosomatic medicine may be doing such cases a disservice by favoring emotional factors as the cause of indigestion. Gastroscopy does not replace but merely supplements X-ray examination.

BOWEL

FORTY, F.: *Leiomyosarcoma of the stomach: thoraco-abdominal gastrectomy*. (Proc. Roy. Soc. Med., Feb. 1948, V. XLI, No. 2, p. 100).

A man aged 66 had noticed, for two months, that food seemed to stick at the level of the lower end of the sternum. Barium was held up at the cardia, and the X-ray appearance suggested a large proliferative growth at the cardia. On laparotomy it was

determined that the mass was mobile and that there were no metastases. The combined thoraco-abdominal approach was used and the upper half of the stomach and lower inch of the esophagus were removed and the esophagus anastomosed to the body of the stomach in the left pleural cavity. He made a good recovery. The specimen showed a leiomyosarcoma of low-grade malignancy.

SUTLER, M. R.: *Endometriosis of intestinal tract*. (Surgery, V. 22, p. 801, Nov. 1947).

Probably the only way of establishing beyond doubt a diagnosis of endometriosis of the bowel is histological examination. This is made necessary because of usually coexisting lesions of the bowel and the fact that in cases of confirmed endometriosis the condition may be silent or found only incidental to operation for other reasons. Endometriosis was diagnosed in 848 out of 140,700 cases in whom histological examinations for diagnoses were made. This is probably much lower than the actual incidence in the female population at large. From eight to 15 per cent of all women during active menstrual life and 10 to 22 per cent of all women undergoing gynecologic surgery by the abdominal route are believed to have endometriosis. Since the intestinal tract is a widespread organ it is to a great degree the site of the extragenital endometriosis. In the present study the appendix was the site in 25 out of 35 cases of endometriosis of the intestine.

LOFSTROM, J. E. AND KOCH, D. A.: *The diagnosis of ascaris infestation by serial roentgen examination of the small intestine*. (Am. J. Roentg. and Rad. Th. 57, 4, 449, April 1947).

In six cases the diagnosis of ascaris infestation was made on the findings of displacement of the barium by the parasite as seen in roentgenograms of the small intestine after ingestion of barium. The sharply outlined linear defect of the exact configuration of a round worm was noted in various portions of the small intestine from the upper jejunum to the lower ileum. In one case only one worm was detected, in another case six worms could be visualized. The size of the worms varied from two cm. to 15 cm. in length. None was detected by fluoroscopy. The 24 hour roentgenograms failed to reveal any barium residue in the intestinal tract of the parasites. The presence of the parasites had no effect on the motility, the lumen or the mucosal pattern of the intestines.

FRANZ J. LUST.

SCHAEFER, A. A. AND ERBES, J.: *Hypertrophic pyloric stenosis*. (Surg. Gynecol. and Obstet., V. 86, p. 45, Jan. 1948).

The authors conclude that physical examination alone is inadequate for proper diagnosis of pyloric stenosis and believe that roentgenologic studies are important for arriving at the correct diagnosis early. During the 23 year period ending May 1947 there were 248 patients admitted to their hospital with pyloric stenosis. Of these 15 were treated medically

with a mortality rate of 46.6 per cent (seven cases). Pyloromyotomy was done in 232 cases with a mortality rate of 6.9 per cent (16 cases). With earlier diagnosis and better post operative care as well as routine blood transfusions and chemotherapy the post operative morbidity and mortality has been greatly reduced.

HODGES, FRED J., RUNDLES, R. WAYNE, AND HANELEN, JOSEPH: *Roentgenologic studies of the small intestine. I. Neoplastic and inflammatory disease.* (Radiology, 49, 5, 587. November 1947).

More and more the importance of the roentgenological examination of the small intestines is recognized. The authors used the following method: after fluoroscopy and roentgenology of stomach and duodenum they took films two and a half hours and five hours after the barium meal. They publish their findings in a number of very interesting cases. They show: primary carcinoma of the jejunum, lymphoblastoma of the duodenum, cases of regional jejunitis, periappendiceal abscess, ulcerative ileo-colitis, and ileo-cecal tuberculosis.

Of special interest is one case who was studied and treated intensively for a period of eight months. At no time was there clinical evidence of specific vitamin deficiency, anemia, or neurologic disease. The roentgenograms showed abnormal dilatations and contractions of stomach, small and large intestines. The small intestines resemble those seen in severe vitamin deficiencies. There was no significant response to therapy. Death eventually occurred as a result of failure of the motor and absorptive functions of the intestinal tract. At necropsy there was extreme atrophy of all the organs, malnutrition, and muscular atrophy with diffuse fibrosis of the entire intestinal tract. Special examination of the central and peripheral nervous system demonstrated profound change. There was an advanced myelin degeneration of spinal cord and the sciatic nerve. The ganglia of Auerbach's plexus were swollen, their neurons were reduced in number, and the perisomatic glia was proliferated. Nerve fibers connecting ganglia exhibited degeneration comparable in severity to that of the sciatic nerve. It is evident that both the central and the peripheral nervous system suffered damage to a degree which was no longer compatible with life. The profound functional disturbance of the intestinal tract as demonstrated roentgenographically appears to be intimately related to the intramural nervous system changes. A satisfactory explanation of the whole course of the patient's illness is not forthcoming. The neurologic changes are particularly engrossing and challenging. At this time one cannot be certain whether they were primary in origin, or secondary to some systemic disorder.

FRANZ J. LUST.

SPENCER, JACK AND THAXTER, LANGDON, T.: *Acute obstruction of the small bowel.* (Radiology, 49, 5, 611. November 1947).

It must be emphasized that there are a large number of cases presenting problems in the diagnosis of obstruction that will require frequent examination of the abdomen, including palpation and auscultation as well as repeated radiographic studies. The selection of cases that have been verified surgically necessarily limits the doubtful cases and allows for a more accurate correlation of the roentgen and operative findings. The radiographic findings were conclusive of obstruction in 94%, the level of obstruction can be localized roentgenographically. The mechanisms of obstruction in two cases of small intestinal obstruction were:

Adhesions with previous laparotomy	55
Adhesions without previous laparotomy	15
Adhesions: previous operation not stated	8
Internal hernia	8
Meckel's diverticulum. Gallstones each	3
Fibroma, causing intussusception	2
Intussusception (one due to carcinoma of cecum)	2
Tuberculous ileitis	1
Terminal ileitis	2
Adhesions (carcinoma not diagnosed previously)	1

FRANZ J. LUST

OSGOOD, ELLIS C.: *The role of the radiologist in the management of patients with intestinal obstruction, with special reference to the use of the Miller-Abbott tube.* (Radiology 49, 5, 529-553. November 1947).

The value of this article lies in the extensive and thorough description of the use of the Miller-Abbott tube in cases of intestinal obstruction. The technique, as given by the author, is comparatively simple. The advantage of the use of the tube is that it often converts an emergency into an elective procedure. The absence of the high degree of distention after treatment, simplifies the surgical procedure.

In cases of mechanical obstruction, the tube may be considered as a useful adjunct. It has proved in reflux ileus to be a therapeutic in itself, since surgical enterostomy is generally conceded to be valueless and sole reliance must be placed on non-surgical decompression. In such situations, the results with the tube have been truly brilliant.

There are few contraindications to the use of the Miller-Abbott tube. It must not be used in persons known to have or suspected of having strangulation or gangrene of the bowel if operation is thus delayed. Its use is also contraindicated in external hernias since some contain strangulated intestinal loops. In cases of obstruction of the large bowel, there is an increase in the tonus of the terminal ileum which makes uncertain and delays the entry of the tip of the tube into the cecum. Besides, the cecal contents are ordinarily too grumous for aspiration through the tube. Diagnostic procedures performed by injection of barium through the Miller-Abbott tube have been described. The author's experience has not established

their indispensability, however. While the studies have demonstrated, again, the physical incompleteness of many small intestinal obstructions, they have not indicated to any significant extent the necessity for operation. In this respect the clinical observations as to whether or not there is a recurrence of intestinal colic and distention after discontinuance of suction have been more important.

As repeated fluoroscopy and roentgenographs are necessary to determine the site of the tube and the type of the obstruction, the Miller-Abbott tube is best used under the supervision of the radiologist.

FRANZ J. LUST.

BAKER, W. T.: *Psychologic aspects of ulcerative colitis*. (Northwest Med., April 1948, V. 47, No. 4, 271-273).

The author apparently favors the hypothesis that ulcerative colitis is a psychogenic disease. He shows that the disease occurs in the dependent, passive, egocentric, immature individual who has a hostile, anxious concept of himself in the scheme of things, who has met with emotional trauma involving love loss and humiliation, but of course does not offer proof of the psychogenic origin of the disease, since this is not at present possible.

MOENE, I.: *Fatal issue of appendectomy caused by Addison's disease*. (Nordisk Med., Mar. 27, 1948, V. 37, No. 13, 643-644).

Appendicectomy was performed on a woman, 27 years of age. She was suspected of chronic appendicitis, but the appendix turned out to be normal. On the day after the operation, the temperature rose sharply to 40° C., and she died two days later in a state of profound shock, with a pulse rate of 144. Sulfathiazol and penicillin were of no benefit. Pigmentation of fingertips and of the furrows of the hands were noticed before death. The post mortem revealed nearly complete destruction of the adrenals by tuberculosis. The blood pressure had not been measured before the operation.

SURENGER, L. A.: *Carcinoma of the large bowel*. (Ill. Med. J. Feb. 1948, V. 93, No. 2, 92-94).

In a review of 237 cases, it was found that 80 per cent of cancers of the colon occurred in the left side of that organ and 45.6 per cent of all the cases were in the rectum. Blood in the stool was noted in about 69 per cent of lesions located in the left side as compared with about 15 per cent of the cases on the right side. Radiation therapy alone had no noticeable effect on the progress of the disease, though the author gives no details as to its application or dosage.

WHITE, R. B.: *Chronic amebiasis of the cecum*. (Illinois Med. J., Feb. 1948, V. 93, No. 2, 102-106).

The cecum is most frequently affected in chronic amebic colitis and X-ray findings are suggestive though

not pathognomonic, — a contracted, shortened deformed cecum which distends and contracts poorly and an incompetent ileo-cecal valve. These changes once having occurred, are probably irreversible, and remain as permanent indications of a past infection.

BARCLAY, T. H. C.: *Observations on the operative treatment of two cases of irreducible intussusception*. (Glasgow Med. J., V. 28, p. 51, Feb. 1947).

Primary resection of the irreducible part of the intestine in children under one year of age is regarded as a dangerous procedure. There appear to be only twenty-one successful cases reported in the literature. In one of the two successful cases reported here an important factor was the decision to operate early without wasting time in attempting manual reduction. Manipulation of the intestine is tolerated poorly and should be reduced to the minimum. Supportive intravenous therapy with glucose and saline before, during and after the operation corrected dehydration.

BLACK, D. A. K., BOUND, J. P., AND FOURMAN, L. P. R.: *Fat absorption in tropical sprue*. (Quant. J. Med., V. 16, p. 99, 1947).

The studies were performed on 28 patients with tropical sprue in its early stage. Percentage fat absorption was designated as the dietary fat minus fecal fat divided by the dietary fat. The fat determinations were made in a series of fat-balance studies. The percentage fat absorption in normal subjects was over 90%, in untreated sprue it varied between 51% and 85%. Neither riboflavin nor nicotinic acid were effective in producing either clinical improvement or improved fat absorption. Liver therapy resulted in weight gain and in clinical improvement; however improvement in fat absorption lagged behind clinical improvement by several weeks.

BASSLER, A. AND PETERS, A.G.: *Sulfonamide therapy of infections of the gastrointestinal tract*. (Rev. Gastroent., Feb. 1948, V. 15, No. 2, 151-158).

The sulfonamides are without value in acute, fulminating ulcerative colitis. They are indicated in regional ileitis where so much gut is involved that surgical removal is impossible. The drug of choice is sulfasuxidine with sulfaguanidine next best. The sulfonamides are of value in bacillary dysentery in all stages.

SEAL, S. C. P.: *Sulfaguanidine in the treatment of cholera under rural conditions, (290 cases)*. (J. Indian Med. Assn., Dec. 1947, V. XVII, No. 3, 85-90).

A study was made of 30 small outbreaks of cholera involving 29 villages in a region of Bengal, India, in 1944-45 with a view to determining the value of sulfaguanidine in such cases under field conditions. Of the total of 290 cases, 134 were treated with the sulfonamide with only two deaths, and 154 cases by other methods with 67 deaths. Initial dose of sulfa-

guanidine — three grams followed by two or three grams every three or four hours until the stools were reduced to two per day or less. In severe cases a total dose of 28 grams was used. No toxic symptoms developed. The drug may safely be kept in stock in every home within the cholera epidemic area and used at least as an emergency or first aid measure.

PANCREAS

BRANFORD, W. V.: *Acute epigastric pain and blood amylase activity.* (Southern Med. and Surg., Feb. 1948, V. 110, No. 2, 41-44).

Acute epigastric pain is significant in the diagnosis of acute pancreatitis, but definite diagnosis is made on increased blood amylase activity. Conservative treatment is recommended and surgery is reserved for those cases with complications.

PITT, D.: *Fibrocytic disease of the pancreas: a review of 14 cases.* (Med. J. Australia, Jan. 24, 1948, V. 1-35, No. 4, 91-100).

Dorothy Anderson's work in America in 1938 is chiefly responsible for this disease having emerged as an entity. The chief features are malnutrition, steatorrhea, and chronic respiratory infection. When the disease develops before birth, the infant dies within two weeks after birth due to intestinal obstruction. The majority of cases developing after birth die before the age of five years. Of the present series of 14 cases, nine have died and five are still receiving treatment. Essentially the disease results from deficiency in the external secretion of the pancreas. The liver most frequently is fatty and enlarged and in some cases a remarkable degree of hepatic cirrhosis is present. A protein rich, high caloric diet, low in fat is required in treatment, as well as pancreatin, vitamin A and chemotherapy of the pulmonary infections.

PAGEL, W. AND WOOLF, A. L.: *Aseptic necrosis of pancreas due to arterial thrombosis in malignant hypertension.* (Brit. Med. Jour., Mar. 6, 1948, 442-443).

It has been sometimes theorized that acute pancreatitis might occur on a vascular basis but the case here reported showed marked arterial thrombosis of the pancreas but neither the clinical or anatomic picture revealed any relationship to acute hemorrhagic pancreatitis or pancreatic fat necrosis. The pancreas was swollen and hardened and presented ten small anemic infarcts and in the center a large area of confluent necrosis. There was no fat necrosis. Apparently the vascular changes in the pancreas were responsible for the epigastric pain experienced by the patient during the last three weeks of his life. He was a man of 45 suffering from malignant hypertension and terminal uremia.

GLENN, JOHN C. AND BAYLIN, GEORGE J.: *Roentgen findings in acute pancreatitis.* (Am. J. Roentgen. and Rad. Th. 57, 5. 604. May 1947).

If there is an appreciable enlargement of the head of the pancreas the duodenal loop may be widened and the valvulae conniventes flattened, and the inverted "3" sign of Frostberg may be evident. There may be a spasm of the duodenal loop. Along with these changes there may be a pressure defect or marked spastic contraction of a portion of the transverse colon, and some of the small intestine of this region may show similar changes; that is alternate spasm and dilatation. The foramen of Winslow may be sealed off isolating the lesser omental sac where large collection of fluid may displace the stomach. An upward displacement of stomach and duodenum is often observed. An extremely important relationship is the diaphragmatic one, for many cases of pancreatitis will show evidence of fluid at the base of the left lung, undoubtedly due to inflammatory changes occurring in the diaphragm or beneath it. Frequently the obliteration of the shadows of the left psoas and kidney is found. Diverticula of the duodenum may be imbedded in the pancreas.

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COLLETT, R. W. AND KENNEDY, R. L. J.: *Chronic relapsing pancreatitis associated with hyperlipemia in an eight year old boy.* (Proc. Staff Meet. Mayo Clinic., March 31, 1948, V. 23, No. 7, 158-162).

Clinically this case resembled chronic relapsing pancreatitis in adults — several major attacks of upper abdominal colic lasting several days, sometimes with shock, sometimes with transient glycosuria. He had been subjected to operation on three occasions and each time a ruptured pancreatic abscess was found and drained. There were also minor attacks of pain at intervals. On examination at a time when he appeared well, high values were found for serum lipase, serum amylase, phospholipids and cholesterol which tended to subside spontaneously. Few similar cases have been reported. Children are subject to pancreatitis with scarlet fever, diphtheria and parotitis. Only two cases of chronic pancreatitis in children were found in the literature. Some of the cases described as "idiopathic hyperlipemia" in children probably were instances of chronic relapsing pancreatitis. In adults high blood values for lipids in pancreatitis are common but not in children.

LIVER AND GALLBLADDER

SHAPIRO, A. L. AND RABILLARD, G. L.: *The arterial blood supply of the common and hepatic ducts with reference to the problems of common duct injuries and repair.* (Surg. V. 23, p. 1, Jan. 1948).

The formation of biliary fistulas, fibrosis and strictures, or a delayed improvement following surgery to the bile ducts, may be attributed to incidental injury to the blood vascular system supplying the ducts. Contrary to accepted views, the authors find the main arterial supply not to be from the hepatic artery but from the cystic artery and the postero-superior pan-

creaticoduodenal artery. The arborization of arterial twigs around the duct make ischemic damage less likely to occur than the cutting of a blood vessel in a duct supplied with only a few arterial branches. The data and illustrations were obtained by the authors after careful dissections of the biliary tree of 23 cadavers.

CARON, W. M.: *Clinical study of acute pancreatitis*. (Laval Med., V. 11, p. 683, 1946.

The author reports a study of twenty cases of acute pancreatitis. In 16 of these patients there were also present dysfunction of the biliary system as shown by cholecystography, exploratory operation and autopsy.

MURPHY, T. L., CHALMERS, T. C. AND ECKHARDT, S.: *A study of forty patients who died in liver coma*. (J. Clin. Invest., V. 26, p. 1191, Nov. 1947).

All forty patients studied at autopsy had had severe primary liver disease. In twenty patients the coma was uncomplicated by any factors, in seventeen others the coma was precipitated by infection and in three by hemorrhage. Clinical and liver function studies performed during coma yielded the same information as those performed before the patients became comatose. Confusion and delirium preceded coma in a number of patients and in these sedatives were used. The sedation merged into coma. It seems probable that without infection, hemorrhage, or use of sedatives the development of coma would have been rare. Supportive therapy may help during confusion and delirium.

MORRISON, L. M.: *Types of cirrhosis of the liver responsive to treatment*. (Rev. Gastroent., Feb. 1948, V. 15, No. 2, 119-132).

Cases of "fatty" cirrhosis of the liver tend to respond to high-protein, high-carbohydrate, low-fat diet, supplemented by parenteral liver extract and oral vitamins, plus choline orally. Fatty cirrhosis appears to be a nutritional deficiency disease, especially when alcoholism and inadequate diet are the etiologic agents. In cases of non-fatty cirrhosis, treatment is less successful and generally a failure.

EDITORIAL: *"The liver and all that."* (New Zealand Med. J., Feb. 1948, V. XLVII, No. 257, 1-3).

The writer remembers how vague our knowledge of the liver was only a few years ago when Boyd, speaking of the behaviour of the liver in the earlier editions of his *Pathology of Internal Diseases* was constrained to apply the remark of Frascatorius on another subject that "it was only to be comprehended by God." While God presumably still has the only perfect comprehension of this amazingly complex subject, the editor emphasizes the importance of diet in liver disease and admits that we know something now about virus hepatitis, and have profited by labora-

tory examinations. Phosphorylation is fundamental, and this requires choline. Malnutrition produces cirrhosis in South Africa. Fulminating hepatic necrosis is due to the lack of cystine. So-called liver function tests such as the thymol turbidity test, the cephalin flocculation test and the Takata-Ara reaction, actually merely demonstrate an alteration in serum protein which is consistently present when the liver parenchyma is primarily attacked. Probably the use of radioactive isotopes as tracers will further assist our growing comprehension of a subject still only encompassed by Deity.

ULCER

FELDMAN, M.: *A statistical study of 112 cases of benign gastric ulceration*. (Am. J. Med. Sci., V. 128, p. 13, Jan. 1948).

In a recent study of 7,300 gastro-intestinal examinations over a ten year period, 1,154 cases of duodenal ulcer and 112 cases of gastric ulceration were observed. Of the latter, 74 involved the cardia and body, and 38 the pylorus. An increase of 0.4 per cent incidence was noted in the civilian population during the war. Sixty of the 74 gastric ulcerations were in males, and the majority were between 30 and 70 years of age. The symptoms had a duration of one month to 40 years, and mostly one to ten years. Recurrences in the 74 cases were infrequent in that the majority had only one severe recurrence up to the time of examination. All the gastric ulcers showed a niche filling defect on X-ray examination. While 66 had pain, only 40 had a food relationship. Vomiting occurred in 18 of the 74 cases, and massive gastric hemorrhage in only four. Most showed occult blood, but only four had black stools. Two gave a history of perforation. Loss of weight (due to food abstinence) occurred in 16 patients. Thirty-six patients were constipated, the remainder were normal. Of the 38 patients with pyloric ulcers, 25 were males. The duration was longer and pain and vomiting were prominent features. Only one case of massive gastric hemorrhage occurred. Pyloric obstruction occurred in seven instances. There were one to four recurrences and no perforations.

KAY, A. W.: *The effect of water on gastric motility — test for duodenal ulcer*. (Lancet, V. 252, p. 448, April 1947).

In patients with peptic ulcer, but not in normal subjects, the ingestion of cold water stimulates gastric motility. In normal subjects the cold water usually inhibits gastric activity. The augmentory response shown by the ulcer patient disappears when the ulcer is healed. The phenomenon is attributed to reflexes from stimulation of the ulcer area by the cold water. Since in normal subjects and patients with gastric ulcer or cancer and patients with biliary tract disease the response is one of inhibition, the cold water ingestion response is suggested as a diagnostic test for peptic ulcer.

SURGERY

MALBIN, MORRIS: *Pseudoneoplasm as a post-appendectomy finding.* (Am. J. Roentgen and Radium Th. 57, 6, 750. June 1948).

The author describes round filling defects at the tip of the cecum as found during the roentgenological examination of the cecum. These defects are due to the procedure of inverting the appendiceal stump after appendectomy. They were demonstrated in four patients and in a post-mortem specimen. In addition, the findings were reproduced by performing appendectomies in two additional postmortem specimens. It is important that these findings are correctly evaluated for true adenomas must be eradicated because of their marked tendency to undergo malignant degeneration.

FRANZ J. LUST.

MONTGOMERY, J. G.: *Simplified repair of the common duct — use of umbrella catheter to produce internal biliary fistula.* (Surg. Gynecol. Obstet., V. 84, p. 321, 1947).

The common duct may be reconstructed so long as a vestige of the common duct remains which can be dilated to receive the head of a catheter. The head is inserted into the proximal end of the common duct through a stab wound. This keeps the tube from slipping. The distal end of the tube is passed into the duodenum through the distal end of the duct or through a stab wound which is small enough to make a tight fitting. The catheter should extend into the duodenum for a short distance so that it will not retract. Silk purse-string sutures may be used. The exposed surface of the catheter tube is covered with fat and viscera so that an internal biliary fistula is constructed. Sulfonamides used topically prevent infection. The catheter tube should not be removed until the biliary fistula is well formed but it is better still to leave it in place permanently.

Ten patients were operated for establishing a biliary fistula in this manner and each resulted in successful relief of jaundice and re-establishment of bile flow. In six patients death was due to metastatic carcinoma. In one patient the catheter remained in position for three years. In another patient the biliary fistula remained patent after two years although the catheter had been extruded by the twelfth week.

EXPERIMENTAL MEDICINE

PHYSIOLOGY

BALLMAN, J. L., FLOCK, E. V. AND BERKSON, J.: *Turnover rate of phospholipid phosphorus in the liver of the white rat.* (Proc. Soc. Exp. Biol. Med., V. 67, p. 308, March 1948).

The phospholipid phosphorus in the liver of the white rat during conditions of equilibrium was investigated to obtain information on the turnover rate. The proportional turnover rate was close to five per cent per hour. The mass turnover rate of hepatic phospholipid phosphorus was found to be six mg. per hour per 100 grams liver or 0.2 mg. per 100 grams body weight.

EDWARDS, C. T. AND EDWARDS, L. E.: *Factors influencing in vitro secretion of pepsin.* (Federation Proceed., V. 7, p. 30, Mar. 1948).

Under suitable conditions the isolated mucosa will live for some time. When clamped between two separate chambers the mucosal side can be made to secrete acid and pepsin by applying appropriate drugs to the serosal side. Experiments indicated that nitrogen-containing compounds were necessary for the production of pepsin and that pepsin was secreted in response to acetylcholine and eserine.

LOMBROSO, C. AND BOCCHIOTTI, S.: *Lipodieresis in liver tissue of depancreatized dogs.* Science, 107, 90, Jan. 23, 1948).

Lipodieresis is the disappearance of part of the lipoids stored in a tissue which has been kept for some time in aseptic autolysis. This apparently reversible phenomenon occurs most markedly in liver tissue. In suspensions of finely chopped liver of the normal dog there may be a decrease in the total lipid content of as much as 20 per cent during autolysis of 30 hours or less. This phenomenon of lipodieresis however does not occur if the liver is derived from depancreatized dogs. However, addition of pancreatic extract to the live tissue of depancreatized dogs restores the phenomenon of lipodieresis.

VARTIAINEN, I. AND BASTMAN-HEISKANEN, L.: *Food selection in alloxan diabetes (Preliminary report).* (Ann. Med. Intern. Fenniae (Finland) V. 36, p. 740, 1947).

Richter's self-selection method was used. Rats were made diabetic with alloxan. A pre-alloxan period of 50 to 100 days served for control. With development of diabetes the ingestion of glucose decreased, markedly in severe cases. Only a few rats showed increase in the amount of fat taken. Appetite for protein (casein or yeast) was increased considerably. In several cases there was a strong craving for potassium, which would suggest that there were changes in adrenal function.

Pruritus in Hepatic Disease

S. E. SCHECHTER, M.D.

and

H. NECHELES, M.D., PH.D., F.A.C.P.

CHICAGO, ILLINOIS

THE PROBLEM of why pruritus occurs with jaundice and with some non-icteric liver diseases has been the subject of much discussion and experimentation. Many mechanisms have been suggested, but none has been proved. No definite correlation has been established with the appearance or the change of any one chemical constituent in the blood. As yet the answer eludes us completely. This is due in part to inability of investigators to objectively evaluate the symptom in experimental animals. Probably however, the greatest obstacle is the complexity of the physiology of itching itself, which remains incompletely understood.

Itching may occur in liver disease unaccompanied by jaundice. It may precede the icterus (in 20% of cases) (1), may occur early or late in association with the jaundice, or may come and go intermittently. When it occurs in infectious hepatitis, it appears early. It is conspicuously absent in hemolytic jaundice. It may be completely relieved following drainage of the gall bladder, even before icterus disappears. This applies to obstructive biliary disease as well as to chronic hepatitis and cirrhosis (2). The figures of different authors vary regarding the frequency of pruritus in liver disease. Rothman and Shapiro (3) state that 20 to 25% of jaundiced patients have pruritus (33% of cases with common duct obstruction; 44% of those with toxic liver disease due to drugs; 14% of cases of acute catarrhal jaundice). Horrall (4) and Lichtman (5) quote various authors: 50 to 60% of cases of common duct stone, more with stricture of the common duct, and 75% with neoplastic obstruction have pruritus; another series reports itching in 41% of cases with malignant obstruction and 21% of cases with benign biliary obstruction. Most writers agree that the pruritus of malignant obstruction is usually more severe than that of other types.

As a preliminary step in a study of the nature of itching in liver disease, we are herein reporting the result of a survey of the whole subject, not only as related to hepatic dysfunction, but also in its broader aspect as a physiological phenomenon. Some of the work quoted here cannot be critically evaluated because it is based either on pure speculation or on obsolete experimental methods. However, a review of the literature is indicated, we believe, to remind investigators of the need for further and more accurate study of the problem.

I. GENERAL FACTORS CONCERNED IN PRURITUS

1. *Histological aspects.* Intact skin from pruritic areas cannot be distinguished microscopically from specimens taken from non-pruritic sites (6).

2. *Neurological aspects.* The sensation of itching arises in the free nerve endings of the epidermis or in the corresponding epithelial layer of transitional mucus membrane. It is impossible to elicit itching from skin denuded of epidermis. Itching is related to protopathic pain (Head, 7), both of these being characterized by poor localization, radiation, poor discrimination between varying intensities of stimulus, persistence of the sensation after stimulation has ceased, and by pronounced discomfort. Superficial tickling progresses to itching and then to pain, as the intensity of the stimulus is gradually increased (6, 8, 9).

Protopathic sensations are mediated by the slowly conducting C fibers (Erlanger and Gasser, 10) and it is the frequency of impulses in these fibers which determines whether itching or pain is perceived. Scratching, pinching, slapping, vigorous rubbing, etc., relieve itching by producing sharp pain. The patient tries to replace the disagreeable protopathic feeling by the less disagreeable epicritic sensation (6).

Sultzberger (11) presents the following evidence for associating itching and pain:

- a. Itching cannot be produced in analgesic areas.
- b. Itching can be produced where pain sense is present but tactile sense absent.
- c. Thermal sense is dissociated from the sense of itching.
- d. Reflex times for pain and itching are identical.
- e. Sensory points for itching seem to coincide in distribution with sensory points for pain.
- f. During anesthesia the susceptibility to pain and itching disappears almost simultaneously.
- g. Hypoalgesic areas, i. e., skin areas with decreased sensitivity to pain, respond with a sensation of itching to a stimulus ordinarily adequate to produce pain.

Stevenson (12) quotes the work of Ehrenwald, who observed patients and experimental animals with dissociated and impaired sensation (as in syringomyelia), and concluded that mechanisms of both pain and touch are necessary to the normal sensation of itching. However, weakened and qualitatively altered itching

From the Department of Gastro-Intestinal Research, Medical Research Institute of Michael Reese Hospital, Chicago, Ill.

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sensations may occur in the absence of pain or touch.

According to Rothman and Shapiro (3), itching has an integrating center in the hypothalamus, the excitability of which can be influenced pharmacologically. The subcortical center is under a higher control in the cortex. In animal experiments, scratch movements become greatly enhanced after bilateral ablation of the frontal cortex. Stevenson (12) states, the central reception point for itching is thought to be in the thalamus.

Rothman (6) further speaks of a scratch center in the medulla below the acoustic meatus, which is concerned with reflex responses.

Sultzberger (11) writes that, while the actual sensation of pruritus is transmitted by the pain-nerve pathways, the susceptibility to this sensation (threshold of irritability) seems to be dependent to an unknown degree on the vegetative nervous system. When an imbalance occurs in this system (vagotonia or sympathicotonia) the threshold is lowered and severe pruritus may be elicited by normal innocuous stimuli — as slight friction or changes of pressure (clothing, etc.), slight changes of temperature (undressing, etc.), and mild chemical stimuli (soap, etc.). The autonomic nervous system of course, is in turn dependent on the psyche and psychic changes (see below).

Aubrun (13) cut cutaneous sensory nerves and found pruritus and hyperesthesia in areas which had a common innervation with the sectioned nerves and neighboring untouched nerves, the latter carrying (the author believes) the abnormal sensations to the nerve centers. If all the nerves to a certain area were cut, there was no pruritus. Aubrun showed that this pruritus is independent of sympathetic innervation. Extirpation of the cervical sympathetic ganglia does not produce pruritus and sympathectomy prior to extirpation of the posterior cervical roots does not modify pruritus and hyperesthesia caused by the latter operation. He says the sensory alteration does not appear to be due to vasomotor changes or to an increased permeability of the capillaries.

Lichtman (14) concluded from the results of ergotamine in the treatment of pruritus in jaundice and uremia (vide infra), that the itching here was due to an "increased irritability of the sympathetic nervous system." Rothman (6) however, states that the role of sympathetic innervation in producing itching has been ruled out.

3. Psychogenic factors. The only itching disease of which the psychosomatic mechanism is clearly understood is so-called cholinergic itching (and/or urticaria). Excitement from almost any cause (including sexual), as well as heat, cold, sunshine, trauma and other physical agents are capable of producing these phenomena. They probably result from an hypersensitivity to acetylcholine, which is released in the skin as a result of one of the above mentioned stimuli — an unusual condition wherein hypersensitivity to a

physiological product exists. The symptoms can be reproduced in susceptible individuals by injection of Mecholyl. Nomland (15) postulates that in the production of urticaria, acetylcholine probably acts through the mediation of H substance, but in producing generalized itching, it must have a direct action on the cholinergic nerves of the skin. The condition is found predominately in young females (3).

Stevenson (12) comments that skin seems to be subjected continually to a large number of itch stimuli which do not provoke the pruritus unless the itch excitability of an area is raised (by some irritating factors, such as a skin disease), or unless the attention is abnormally focused on them. Distracting influences usually keep the sensation out of consciousness.

Finally in this category one must mention the purely functional pruritides (psychosomatic, hysterical, etc.) where no organic etiology can be discovered (16).

4. Allergic factors (the H substance, etc.). Sir Thomas Lewis believed that itching is produced by liberation of some cellular product from injured tissues. He quoted evidence which suggests that H substance is involved in the production of the itching in damaged tissues, as in the production of the triple response. Lewis inclined to the view that itching and pain are separate sensations produced by the release of different cell substances, the first of which is set free by slight stimuli and causes itching and the triple response, the second of which is released by more severe injuries and gives rise to pain (17).

Rothman and Shapiro (3) describe two types of allergic itching: 1. the eczematous type: where the reaction takes place in cells of the epidermis. This is usually caused by outside allergens (as in contact dermatitis). 2. the urticarial type: where reaction occurs in the walls of blood vessels of the dermis, probably in the endothelial cells. An urticarial wheal forms, or in reactions of lesser intensity, an erythematous papule. This type is usually caused by allergens reaching the skin via the blood stream. Both epidermal and dermal hypersensitivity reactions in lower intensities may be manifested as pure itching without visible changes; irritating substances may stimulate nerve endings, causing itching without causing cellular damage which would lead to visible changes. Rothman (6) also cites the work of Klinkert who states that pruritus may be the first or even the only symptom of systemic anaphylactic shock in animal experiments as well as in human beings. Klauder (1) confirms this, saying that in experimental anaphylaxis, itching of the animal (guinea pig) is a cardinal and early symptom of anaphylactic shock. While we have observed this phenomenon frequently, we are not convinced that the motion of the front legs in an animal with bronchospasm denotes itching.

5. Miscellaneous factors:

a. Tissue anoxia. This phenomenon may cause pruritus as in vascular disturbances producing stasis (i. e. in lower extremities with severe varicose and thrombosed veins, etc.) (3).

b. *Asteatosis*. Maintenance of the so-called "eudermie" of Jacquet (quoted by 3) requires the greasy covering of the skin supplied by sebaceous glands. Absence of the covering may cause itching. Variations in this greasy coating may be due to a number of factors such as endocrine imbalance (vide infra), too much washing, etc. (3, 16).

c. *Malignancy*. Generalized pruritus associated with neoplasms in various parts of the body has been reported (1, 3). A case of carcinoma of the stomach with generalized itching is cited by Rothman and Shapiro (3). After gastrectomy the itching was suddenly and permanently relieved. This phenomenon occurs more frequently with cancer of the gastrointestinal tract than with neoplasms in other locations. In cases of cancer of the pancreas, itching may be the first symptom. It has been postulated that some toxic product formed by the tumor causes the itching. In some cases, metastases to the skin may be a factor.

In this connection, pruritus due to Hodgkin's disease, leukemia, mycosis fungoides, and other lymphoblastomata must be mentioned. Rothman says that 25% of all cases of mycosis fungoides and Hodgkin's disease start with pruritus as the first symptom. In the late stages of lymphoblastic skin disease, only cases of Hodgkin's continue to itch. The others usually have this symptom only in the early stages (3).

d. *Electrolyte balance*. Klauder (1) speaks of work he has done which indicates that irritability of skin is governed by the calcium/potassium ratio. This he says is controlled by the sympathetic nervous system and is influenced by an interplay of other factors. Sultzberger (11) also mentions the effect upon the skin of local and generalized chemical changes, such as colloidal states and the ratio of anions to cations (i. e. ratio of K^+ , Mg^{++} , Na^+ , Ca^{++} , NH_4^+ , etc., to Cl^- , Br^- , I^- , etc.).

e. *Endocrine factors*. Several authors (1, 3) speak vaguely of hormonal influences in the production of itching. Rothman mentions this in connection with asteatosis. Sultzberger brings up this mechanism in connection with influences playing upon the psyche and on the autonomic nervous system. Further discussion on this point will be found below in connection with effects of liver disease on endocrine balance.

II. FACTORS SPECIFICALLY RELATED TO THE PRURITUS OF JAUNDICE AND OTHER LIVER DISEASES.

Unfortunately, most of the literature dealing with the investigation of pruritus in hepatic disease has been reported in the older literature. In recent years, since the advent of newer and more accurate chemical methods, not much has been done (or at least not reported) on the relationship between pruritus and chemical constituents in the blood which are regulated by the liver. Consequently some of the work which we mention here must not be considered as final.

One fact seems to have been overlooked in all of the studies that have been done. That is that the con-

centration of a substance in the tissues may not be directly related to its blood level. Therefore, it may be that the study of tissue concentrations of various substances may contribute to a solution of the problem.

In general, one may say that there is a rough correlation between pruritus and biliary obstruction. However, as previously mentioned, there are a great many exceptions to this rule. A great many substances whose level in the blood rises with biliary obstruction (intra- or extra-hepatic) have been investigated:

Bilirubin is the one bile pigment which chiefly has been investigated as a cause of pruritus. It seems fairly well agreed that an increase of blood bilirubin alone is not responsible for the itching (18, 19). Other porphyrins have been investigated and also apparently are not responsible (20). Hematoporphyrin may be the cause of itching when the skin is exposed to sunlight or, more probably the itching may be secondary to destructive and inflammatory processes. Pruritus of jaundice is usually more intense at night when the skin is covered and sunlight does not affect it (4).

The bile acids or salts have been considered by many as the cause of pruritus, largely due to the influence of the French School (4). Rowntree et al. (21) however, in 1927, were unable to correlate the presence of itching with elevated bile salt levels in the blood. More recently, Brulé and Cottet (19) reviewed this subject, and on the basis of their work and that of others, concluded that bile salts were not responsible. Lichtman (5) questions the adequacy of methods of analysis of bile salts and says the final word on this particular phase of the problem must await improvement of these techniques. He states that an increase in bile salts in the blood is probably one factor (among others) in pruritus, because of uniformly normal values in hemolytic jaundice where there is no itching, and frequent bile salt retention in obstructive jaundice where pruritus is so often found. To complicate things still further Horrell (4) cites a case of chronic vesiculo-erythematous eruption, in which intense itching was relieved by the injection of bile salts. Others (19) have applied bile salts in ointment form to pruritic areas in various skin diseases. The intensity of the itching was not increased but instead was frequently diminished.

Cholesterol was thought to be a toxic substance many years ago (22). Rosenthal (20) and Snell (23) could find no significant relationship between cholesterol values (high and low) in 60% of 43 cases of generalized pruritus (in which diabetes and uremia had been ruled out). Her criteria and methods need evaluation however.

Although the direct causal relationship of *cholinesterase* to pruritus has never been suggested, the blood levels of this substance have been studied in this connection. Antopol et al. (25) found depressed serum cholinesterase activity in patients with jaundice and biliary tract disease. They stated that bile salts caused inhibition of enzymatic hydrolysis. McArdle

(26), however, reported normal values of cholinesterase in obstructive jaundice, whereas in jaundice of hepatic origin, his values were low. Lichtman (5) on the basis of the work of Antopol et al. suggests that the disturbance in this enzyme system with its resultant imbalance of the autonomic nervous system may play a part in the itching problem.

The steroid hormones are normally destroyed partly by the liver (27) and the effects of their increase in long standing liver disease (i. e. loss of hair and gynecomastia in males with cirrhosis) are well known. Since the role of endocrine factors in pruritus has been considered (1, 3) further investigation along these lines should be undertaken.

Other miscellaneous factors in liver disease which have been suggested as possible etiological agents in pruritus (but which remain unproved) are:

1. Production of abnormal substances in the bowel due to the absence of bile in the intestine, and their absorption into the blood stream (4).
2. Formation of toxic substances in the liver, or lack of detoxification of toxic substances such as intermediary carbohydrate and protein metabolites, or abnormal decomposition products (14, 19).
3. Disturbances in vitamin B metabolism (5).
4. Release of histamine or a histamine-like substance from injured hepatic tissue (5).
5. Increased irritability of sympathetic nerve endings due to one or more of the above factors (5).
6. Increased peripheral blood flow due to one or more of above factors. Lichtman (5) postulates that an increased peripheral blood flow plus an increase in bile salts in the blood, together may be responsible for itching.

USE OF DRUGS IN PRURITUS

A number of drugs have been reported to be of value in the treatment of pruritus and, in the hope that something of the etiology of pruritus could be learned from a survey of these, the literature on this subject was reviewed.

Lichtman (14) has advocated the use of ergotamine tartrate in the itching of jaundice. This is based on the hypothesis that an increased irritability of the sympathetic nervous system is responsible for the pruritus. Since this drug depresses the receptive mechanism of organs innervated by adrenergic nerves, this author tried it and reported good results. Goodman and Gilman (28) state however, that the mechanism of anti-pruritic action of ergotamine is unknown and that the theory of its action on sensory nerve endings seems improbable. Because of the dangers of ergotism, they do not believe it should be used in this connection.

Epinephrine, a sympathomimetic, and atropine, a parasympatholytic drug have occasionally been found of value (3). Pilocarpine, a parasympathomimetic

has also been efficacious at times. It has been suggested that the mechanism of relief with the latter drug may be due to sweating or to slight changes in the cutaneous circulation (28). A number of other drugs, having in common the property of relaxing smooth muscle (especially blood vessels) have been used with good effect at times in generalized pruritus. Among these are aminophylline (29), papaverine (30) and various nitrites (31). Calcium salts (5) and sodium thiosulfate (23) have also been recommended.

The use of intravenous procaine has been reported as being of value in the relief of itching (32). Whether its effect is due to action on nerve endings alone or to some other mechanism, is not known.

Histamine has been given (subcutaneously) for the treatment of pruritus (33). The number of cases in this series was small however, and the results quite variable, although several patients did obtain lasting relief. If it is true that some cases of itching are due to increased amounts of histamine (or H-substance) being released in the skin, then one may postulate that a series of histamine injections may be of value in "desensitizing" or raising the histamine tolerance of the individual. This theory has been tested with varied success in migraine, Menière's disease, histaminic cephalgia, and peptic ulcer.

The new anti-histaminic drugs are receiving wide clinical trial in all allergic and questionably allergic phenomena. Conflicting reports are found concerning their use in pruritus of all types. Feinberg and Bernstein (34) make mention of evidence that these drugs relieve not only the itching of allergic dermatoses but also in some non-allergic states, such as jaundice or diabetes. Parrott (35), working with several anti-histaminic substances, has found one that suppresses pruritus of various etiologies. O'Leary and Farber (36) however, state that Benadryl is not an effective antipruritic and that it brought relief in only 6 of 39 patients with itching of various causes (contact dermatitis, jaundice, toxic pruritus, psoriasis, dermatitis herpetiformis, neurogenic pruritus, etc.).

Thus the drug therapy of generalized pruritus seems to be largely empiric. Drugs with strikingly different and even opposing actions have given good results in some cases. It may be that those drugs which affect the cutaneous circulation may be efficacious just because they produce a change in the peripheral vascular bed, and that any change whatsoever, whether it be dilatation or constriction of the cutaneous vessels, may be enough to bring relief. In any case, the review of these drugs which have been used, throws no light on the mechanisms of pruritus.

In summary, we feel that this review of the literature reveals little that can be used as a starting point for the solution of the problem of pruritus in liver disease. Re-investigation of certain results with newer methods may be one way. It is felt however, that an entirely different and novel approach to the problem has to be sought.

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Problems in the Diagnosis and Treatment of the Non-Calculous Gall Bladder

By

HARRY L. SEGAL, M.D.,

HAROLD A. FRIEDMAN, M.D.

and

JAMES S. WATSON, JR., M.D.

ROCHESTER, N. Y.

THE TERM NON-CALCULOUS GALL BLADDER designates a gall bladder which is the cause of abdominal distress without the presence of calculi either in the gall bladder itself or in its afferent or efferent tributaries. As a matter of fact, disease may or may not be present in such a gall bladder. The first problem thus

presenting itself is to be certain that such a gall bladder is involved in the mechanism producing the so-called gall bladder syndrome.

The gall bladder is merely part of a system by means of which dilute bile from the liver reaches the duodenum in a concentrated form. It is affected, comparable to other hollow organs of the gastro-intestinal tract, by exogenous stimuli from both nerves and hormones as well as by anatomical and physiological

From the Departments of Medicine and Roentgenology, the University of Rochester School of Medicine and Dentistry, Rochester, N. Y.

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derangements, not only in itself but also in the liver, pancreas, and gastro-intestinal tract.

Since anatomical and physiological disorders can be the mechanisms that initiate gall bladder disease and its chain of complications, emphasis is placed upon recognizing and treating correctly the gall bladder syndrome and its cause before disease has become established, or if already present, before irreparable damage has occurred. To accomplish this, the physiology of the gall bladder, the factors that may initiate changes or disease in it, and the rationale of therapy must be understood.

The main function of the gall bladder is to concentrate and store bile for the ultimate purpose of digestion. This concentrated bile is evacuated as a result of a reciprocal reflex mechanism which synchronizes contraction of the gall bladder and relaxation of the sphincter of Oddi. Cholecystokinin is the hormone that initiates this reflex. Fat and to a lesser extent proteins and hydrochloric acid release this hormone from the duodenum.

Two phases of gall bladder contractions have been suggested: (1, 2) the initial phase (cephalic) of short duration, which is under nervous control, and the second phase (hormonal), which is prolonged and regulated by cholecystokinin.

The bile constituents are bile salts, bile pigments, cholesterol, lecithin, water, bicarbonates, and traces of bile acids and calcium. The normal concentration results from absorption of water, chlorides, and bicarbonates.

The most important constituents of bile in relationship to the digestive tract are the bile salts. The function of the bile salts and the entero-hepatic bile acid circulation will be discussed under therapy.

The factors that produce gall bladder derangement have been studied by numerous observers. Russell, Carter and Oppenheim (3) have drawn a graphic picture of these factors. Their conception has been based upon a thorough study and their ideas will be freely used in this discussion.

The history, roentgenologic examination, and duodenal drainage are the important means by which the diagnosis of gall bladder disturbance and its cause are made. The evaluation of the urobilinogen and bilirubin contents in the urine and the icteric index and direct Van den Bergh reactions of the blood may show the presence of complications.

Duodenal drainage first described by Lyon (4, 5) is now a more or less accepted diagnostic aid (6). The occurrence of cholesterol crystals and/or calcium bilirubinate granules means that at least stasis is present, even if no stones have yet formed. The importance of bile drainage will depend upon the experience of the individual responsible for this examination.

The appearance of increased urobilinogen and of bilirubin in the urine, an increased icteric index, and

a direct Van den Bergh in the blood in the presence of the gall bladder syndrome will mean either that an infection, an obstruction, or both are or have been present.

A brief discussion of the mechanism probably responsible for these pigment findings is in order. According to Rich's (7) conception of regurgitation and retention jaundice, it is possible to explain the changes in bile pigments in the urine and blood on the basis of a regurgitation type of subclinical jaundice. Watson and Hoffbauer (8) are of the opinion that the regurgitation of bile even in some cases of hepatitis may be due chiefly to increased permeability of the cholangioles. Since cholangitis and hepatitis (9, 10) may occur secondary to chronic cholecystitis, usually but not necessarily with obstruction, it is conceivable that a comparable biliary disturbance may take place. Some authorities (11, 12, 13) doubt that hepatitis results from gall bladder disease *per se*.

For a more detailed description of the bile circulation, the various tests and their significance, as well as an excellent review of the important literature, Young's (14) discussion of current concepts of jaundice should be read.

Regurgitation jaundice is characterized by the escape into the circulation of the constituents of the bile, which means bile salts, bile pigments, urobilinogen, cholesterol, and so forth. It should be emphasized that in regurgitation jaundice the bilirubin that re-enters the blood has been separated from globin by passage through the liver cells. This regurgitated bilirubin, because it is probably in the form of sodium bilirubinate, does not recombine with globin in the circulation and readily passes the renal filter to be excreted in the urine. Thus the examination of the urine may show an excess bilirubinate. The urine may also contain an excess of urobilinogen. The direct and total Van den Bergh tests of the blood and the modified Harrison's barium chloride test (15, 16) for bilirubin in the urine will show any increase of regurgitated bilirubin in the blood and urine. The urobilinogen can also be studied in the urine by simplified methods (17).

Russell (3) and his associates have divided gall bladder disorders into three main groups:

GROUP I.

DISORDERS RESULTING IN DISTURBANCES IN FILLING

AND EMPTYING MECHANISM OF GALL BLADDER

A. ANATOMICAL CAUSES (MECHANICAL)

1. External — Congenital or acquired
 - (a) Adhesions — Congenital or Inflammatory
 - (b) Abnormal Cystic Artery
 - (c) Pancreatic Inflammation — Edema, Fibrosis with Common Duct Involvement
 - (d) Tumors of Pancreas and Extra-Hepatic Bile Ducts
2. Internal — All Congenital
 - (a) Convoluted Cystic Duct — Valve of Heister Obstruction
 - (b) Septa — "Phrygian Cap"

B. PHYSIOLOGICAL CAUSES (FUNCTIONAL)

1. Hypertonic Dyssynergia
2. Hypotonic Dyssynergia

GROUP II.

DISORDERS RESULTING IN DISTURBANCES IN THE CONCENTRATING FUNCTION OF THE GALL BLADDER

1. Infections cholecystitis
2. Reflux pancreatic juice
3. Abnormal concentration of special elements
 - (a) Bile salts
 - (b) Calcium — Calcified Gall Bladder Wall
 - (c) Calcium Carbonate — "Milk of Calcium" Gall Bladder
 - (d) Cholesterol — Cholesterosis

GROUP III.

DISORDERS IN BLOOD AND METABOLISM RESULTING IN DISTURBANCES OF THE GALLBLADDER

1. Hemolytic Jaundice
Congenital hemolytic icterus, "sickle cell" anemia, etc.
2. Cholesterol Metabolism
 - (a) Pregnancy
 - (b) Obesity

In Group I, the mechanism involved in the anatomical disturbances can be readily visualized. The diagnosis suggests itself in a patient with irregular attacks of colicky pains, or with a burning or tugging sensation in the right upper quadrant. These symptoms are due to the partial obstruction to the normal emptying of the gall bladder. The roentgenogram may be of aid if it shows a small densely concentrated gall bladder with no visualization of the cystic duct. The duodenal drainage will be of aid only after stasis or infection has occurred.

The physiological or functional derangements called biliary dyssynergia or dyskinesia, were first emphasized by Westphal (18) in 1926. It was described as a mechanism resulting from disturbed normal emptying function of the gall bladder, that is, instead of the sphincter or ampulla relaxing when the gall bladder contracts, it stays in spasm with resulting increase in the distending pressure in the gall bladder itself. This produces symptoms of pain, fullness, and so forth. There is adequate evidence to justify this view. Such a disturbance can result from psychogenic factors, comparable to pylorospasm or cardiospasm. Intrinsic gall bladder disease and reflex disturbances from diseases in other gastro-intestinal organs may produce biliary dyskinesia. When present, it is usually in the highly nervous, irritable type of individual and may be associated with a hypertonic stomach, excessive acid secretion, and so forth.

The hypotonic type of dyssynergia, or the "lazy gall bladder," may be due to a lack of good elastic tissue, adequate musculature, or simply a part of a constitutional or endocrine disturbance such as hypothy-

roidism and so forth. It usually occurs in the slower individual with poor general body tone and the obese person, and may be associated with decreased or absent normal hydrochloric acid and possibly decreased or absent normal hormone mechanism.

Portis (19) described an emotional gall bladder disturbance which results in an associated duodenal stasis, regurgitation of bile into the stomach, bitter taste, fullness, distention of abdomen, and so forth.

The patients with hypertonic dyskinesia may have a definite psychic background with attacks of colicky pain in the right upper quadrant or epigastrium. The fact that amyl nitrite may give instant relief can be used as a diagnostic procedure. The roentgenogram shows normal concentration with delayed evacuation, which may be improved by correctly timing the use of amyl nitrite. The gastro-intestinal series will show irritability and possibly changes in the duodenal pattern consistent with the so-called diagnosis of duodenitis. The gastric analysis will present an increased acidity. The duodenal drainage may show irregular response to olive oil. The sediment will be essentially negative in the early stages. If this condition persists, stasis and infection may occur. The duodenal drainage will then contain cholesterol and/or calcium bilirubinate granules and bacteria.

In the patient with hypotonic dyssynergia, the site of dysfunction lies in the gall bladder and not in the sphincter. The patient often shows other evidence of hypotonia such as low basal metabolism rate, low or absent hydrochloric acid, hypercholesteremia, etc. These patients complain not of colicky pain but of mild discomfort in the upper quadrant associated with belching and distention after meals. It is this patient who may be treated merely for a "colon or stomach condition."

The roentgenogram in such a patient shows concentration of the dye with delayed evacuation. Duodenal drainage will reveal dark bile only after the administration of olive oil and not following the use of magnesium sulphate. Large numbers of cholesterol crystals may be present in this bile which may indicate an abnormal relationship between the concentration of cholesterol and bile salts. If no free acid is present, the culture may demonstrate the same flora as that present in the nose and throat and not necessarily indicate infection. If not treated, this gall bladder may develop stones and infection.

The patients described under Group II, in whom the predominating objective finding is a disturbance in the concentrating function of the gall bladder, comprise those cases in which cholecystitis has occurred for one of three reasons, either primary infection, or a chemical inflammation secondary to reflux of the pancreatic juice, or abnormal concentration of special elements, as bile salts, calcium or cholesterol.

Infectious cholecystitis due to a primary bacterial infection occurred in about 10% of the patients studied by Russell and his associates (3). The presence of

any such initiating factor described under Group 1 arbitrarily classifies the patient in that group with disorders in the filling and emptying mechanism with secondary infection and not in this group. If a primary bacterial infection is present, the infection may have reached the gall bladder via the blood or through the lymphatics from some other intra-abdominal focus.

This type of infections cholecystitis may be characterized by attacks of: low grade inflammatory pain of three to seven days duration with tenderness and rigidity in the right upper quadrant during the acute phase; faint or absent visualization of the gall bladder on roentgenography; crystalline sediment of calcium bilirubinate on duodenal drainage; positive culture in the duodenal bile. The organisms claimed to be found most commonly are *B. coli*, *B. typhosis*, *B. Friedlander*, and less commonly, the streptococcus and staphylococcus groups. The failure to apply proper management may result in pigment stone formation, secondary infection of the liver, biliary tract or both. Urobilinogen and bilirubin in the urine or an increased icteric index with a direct Van den Bergh reaction may then be present.

The symptoms of inflammatory gall bladder disease produced by chemical cause resembles those of bacterial inflammation. The history, roentgenogram and duodenal drainage findings will be comparable to those already described with infectious cholecystitis. The possibility of reflux of the pancreatic juice regardless of its effect upon the gall bladder wall has been definitely established. It can occur in patients with either organic or functional obstruction of the common duct in whom the pancreatic duct unites with the common duct above the sphincter of Oddi. This happens in 45 to 84 per cent of people according to various authorities.

Excessive concentration of bile salts may produce irritation with resulting inflammation of the gall bladder. The exact mode of action to produce this situation is not definitely known. The effect can be inflammation which can lead to gangrene of the gall bladder wall.

Calcium derangement may affect the gall bladder in two ways. It can result in a calcified organ wall or calcium may be precipitated in the cavity as carbonate in a putty-like form called milk of calcium. Both types of calcium disorders belong in the calculous group.

Disturbance of concentration of the gall bladder due to cholesterol deposited in the mucous membrane of the gall bladder is called cholesterosis. Its cause is unknown. Detachment of the mucosal tissue containing the cholesterol may form the center for stone formation. The history is not distinctive. The roentgenogram shows normal visualization with rapid emptying of the gall bladder after a fatty meal. A duodenal drainage may not be significant, and the culture of the duodenal specimen is usually sterile. This diagnosis is usually not made preoperatively.

Disturbances in blood and metabolism can produce gall bladder disease. In hemolytic jaundices, sickle cell anemias, etc., an increased destruction of

red cells results in an excess of bile pigments in the bile contents. These tend to precipitate and form calcium bilirubinate stones. Russell and his group (3) state that pigment stones have been found in the gall bladder and biliary tract in 60 per cent of cases with congenital hemolytic icterus.

Gall bladder trouble due to pregnancy and obesity probably is based upon an abnormal cholesterol metabolism. In pregnancy, it is also thought that the gall bladder is less responsive to the stimulating action of cholecystokinin. Two factors, stasis and a relative preponderance of cholesterol in the bile, predispose to precipitation of crystals and the formation of cholesterol stones.

In obesity the static factor may be the consequence of a so-called lazy gall bladder or what is also known as hypotonic dysynergia.

TREATMENT

The therapy of the disturbed non-calculous gall bladder will depend upon the type of disorder and the presence of complications secondary to the initiating cause, that is, whether stasis or infection has already occurred.

In disturbances of the filling and emptying mechanism of the gall bladder the treatment will depend upon whether the cause is anatomical or physiological. If the presence of adhesions, an abnormal cystic artery or cystic duct could be diagnosed with certainty, it is conceivable that a non-surgical regimen would not produce an ultimate cure. However, medical treatment in such cases may be worthy of a trial. The diagnosis though highly suggestible is not positive until operation has been performed and even if the diagnosis were positive, medical trial might be justifiable if the physician and patient were willing to exert the necessary efforts. If strict adherence to a medical regimen prevented symptoms, stasis, and infection, it could be postulated that the mechanical effect was not severe enough to require surgery. If regardless of such a regimen, symptoms persisted, and repeated duodenal drainages showed the presence of crystals, surgical treatment would be definitely indicated. To temporize with medical care under such circumstances would only invite the possibility of complicating factors.

Disorders due to physiological, that is, functional causes require medical care unless the initiating factors have persisted, and have produced marked stasis and infection. Medical treatment is indicated in such patients because the functional disturbance will continue even after removal of the gall bladder. In the case of hypertonic dysynergia, it is the physician's duty to try to learn whether psychogenic or reflex factors underlying the spasm of the sphincter of Oddi can be removed.

Functional hypotonic dysynergia is likewise an indication for a medical regimen. Obesity and other metabolic disturbances, as subnormal action of the thyroid, are to be sought and treated adequately.

Surgery will only be indicated if severe stasis and secondary infection have taken place.

Cholecystitis caused by the abnormal concentration of special elements, as bile salts and calcium, will most likely, in our present state of knowledge, require surgery.

In a majority of acute cholecystitis patients, the underlying mechanism is the presence of one or more stones frequently with an impaction in the cystic or common duct. There is, however, a group of patients with acute cholecystitis in whom no calculi are present. Such an acute disease may be due to reflux of pancreatic ferments, excessive bile salt concentration, or recurrent primary bacterial involvement.

The management of an acute cholecystitis is usually not a question of whether surgical intervention is indicated but when. Because no two patients present the same problem, no hard and fast rule can be formulated. Such a patient must be observed very carefully in a hospital. If the symptoms do not abate rapidly or signs of peritoneal irritation are present, surgery should not be delayed. The management is then comparable to that of an acute appendicitis. With the present surgical and medical standards, including the administration of penicillin, there is no reason in surgical procrastination with a rapidly progressing acute gall bladder. The present criteria for operation cannot be based upon the statistics of the past.

Medical management, when chosen, will vary somewhat with the type of the gall bladder disturbance. Medical treatment is mainly thought of in terms of diet, bile salts and drugs for symptomatic relief. The patient, as a whole, psychogenically and so forth, must also be considered.

The important food in the diet therapy is fat. The old universal rule of a low fat diet has been replaced by the use of fat as indicated by the effect of the fat upon the symptoms. The type of fat and its preparation by cooking has some importance. It is generally thought that fat which melts at body temperature is more readily emulsified and absorbed by the gastrointestinal tract. Thus vegetable fats are readily digestible and butter, cream, and eggs are more easily tolerated than meat fats.

The amount of fat used will depend upon the type of gall bladder disease and the resulting effect upon symptoms. If any obstruction impedes the smooth working of the emptying mechanism, pains may result and fat in the diet may have to be decreased. The quantity of fat handled without symptoms may also rest upon the aggregate of bile salts in the entero-hepatic circulation reaching the intestinal tract. The fat digestion may be indirectly affected by pancreatic disturbance secondary to the gall bladder disease. The lack of bile salts or pancreatic enzymes may be circumvented by the use of bile salts and lipase enzyme.*

The rationale of bile salts in gall bladder disease

* Lipase enzyme made by Upjohn Company is now under investigation.

has received notable discussion. In considering their use in the non-calculous gall bladder, a brief resume of the entero-hepatic bile acid circulation is indicated. This circulation has been known for a considerable time and has been excellently reviewed by Whipple (20) in 1922, and by Josephson (21) in 1941.

The bile acids are formed by the liver cells. Normally the major part of the circulating bile acids seem to be conjugated, that is, the molecule of cholic acid or related compounds such as deoxycholic acid is coupled to glycine or taurine by a peptic linkage. The bile acids are then converted into sodium salts. They pass into the gall bladder as constituents of the bile. The gall bladder concentrates the bile and ejects it into the duodenum intermittently. Bile salts in this concentrated form is better able to aid in the emulsification of fat. When the fatty acids and lipoids combined with bile salts are absorbed in the small intestine, the combination is dissociated in the mucosa cells. The fats are carried further mainly by the lymph, and some directly by the portal system. The bile salts, however, have a tendency to adhere to the intestinal wall where they combine with new fats.

The bile salts are gradually resorbed and are transported directly to the liver by the portal blood, and again excreted into the bile. The same amount of bile salt may be used again and again for the resorption of fats, vitamins or lipoids. In man, the bile salts seem to pass the circulation about three times and in dogs about seven times. Only a small amount of bile salts are lost during the normal circulation. The exact fate of the lost bile salts is not known. It is probably mainly through the feces, and to a smaller extent through the kidney or possibly by destruction in the body. Equilibrium is maintained by synthesis of bile acids probably paralleling the rate of the fecal loss. The endogenous bile salt production of fistula dogs has been found by Smith, Groth, and Whipple (22) to be about 100 mgm. per 24 hours and per kilogram body-weight. In man, Josephson and Larsson (mentioned by Josephson) found endogenous 24-hour production of cholic acids to be 0.7 to 2.0 grams.

If bile salts or acids are supplied either by mouth or intravenously to healthy men or animals, they very soon enter the normal entero-hepatic circulation. The injected or ingested bile salts disappear rapidly from the blood and this is normally followed by an almost quantitative excretion by the liver (at least 90%). The bile volume also increases, which seems to have the effect of keeping the bile salt concentration rather constant. This choleric effect of bile salts is probably the most important regulator of bile volume and bile output under physiological conditions. However, Doubilet (23) found that this volume regulatory effect was different for the various bile acids. In bile fistula dogs, he obtained the most concentrated bile after administration of salts from dog bile. The concentration decreased in the following order: ox bile, glyco-cholic, cholic, deoxycholic and dehydrocholic acid. This order is also the order of toxicity of the bile acids (Gilbert, 1926, quoted by Josephson).

Schmidt, Beazell, Berinan, Ivy and Atkinson (24) tested the effect of various commercial bile acid preparations. They found that the conjugated bile acid preparations proved superior as stimulants to the flow of bile containing a rich amount of biliary constituents. The oxidized unconjugated preparations increased mainly the aqueous fraction of bile.

In the regurgitation type of jaundice, due to an obstruction of the common duct, the bile salts are absent or decreased in the intestinal tract and re-enter the blood circulation through the cholangioles, lymph spaces and thoracic duct, or by means of diffusion through the sinusoids. In acute cholecystitis or cholangitis, Doubilet and Colp (25) found that about nine-tenth of the bile salts, especially the cholates, were reabsorbed from the gall bladder and the bile ducts and again carried to the liver. In chronic cholecystitis about 50% of the bile salts were reabsorbed. If liver damage is present, it is conceivable that some of the bile salts can re-enter the blood circulation through the damaged cholangioles in the same manner as described for the regurgitation jaundice due to an obstruction.

The indication for bile salt therapy in the non-calculous gall bladder disease will depend upon the type of disturbance.

If the bile salts in the entero-hepatic bile acid system is not being diverted or exhausted by a regurgitation type of jaundice or by actual cholecystitis sufficient amount of bile salts is probably available. However, even with a normal bile acid circulation, it is conceivable that in the mechanical or hypotonic type of gall bladder disturbance an increased amount of bile salts in the bile may prevent cholesterol from being precipitated and thus help to prevent stone formation and secondary infection.

If chronic cholecystitis should be present, some of the bile salts may be absorbed by the diseased gall bladder as shown by Doubilet and Colp (25) with a resulting diminution of bile salts in the intestinal part of the entero-hepatic circulation. This suggests that bile salts are indicated in the therapy of chronic cholecystitis in which the gall bladder still takes an active part in the entero-hepatic circulation.

In later stages of gall bladder disease, there may be certain conditions in which surgery is inadvisable, or even after surgery has been performed, damage to the liver may be present with resulting loss of bile through the injured cholangioles. Some of the bile acid may be excreted in the urine or destroyed in the body and not necessarily re-enter the bile circulation. Under such circumstances it is possible that the bile salts will be decreased in the intestinal tract with consequent interference with fat digestion and with the other functions that bile acids perform. This situation should recommend the use of bile salts.

Many therapeutic preparations of bile, and bile salts are available, such as dried ox or hog's bile, the nat-

ural ox bile salts with or without iron and the oxidized bile salts or acids. Their action and possible toxicity has been discussed by Ivy and Berman (26). Sodium taurocholate and extract of ox bile are natural unoxidized conjugated bile salts. Bilron is an example of a natural bile salt containing iron. Ketochol represents an oxidized, unconjugated bile acid preparation. Decholin is an oxidized unconjugated bile salt.

The selection of a bile salt for therapeutic purpose is not as simple as it might seem. However, certain rough principles may be established for the present which may have to be changed as a result of further experimental investigation. If merely a flushing action of the bile acids is needed, it would appear logical to use the oxidized, unconjugated bile salt preparations. If an increase in the concentration of the bile salts is desired, then the unoxidized conjugated bile salts seem preferable. If the soluble type of bile salts seem to disturb the stomach, the unoxidized conjugated iron bile salts which are insoluble in an acid medium should be administered. Perhaps it might be best to say that if bile salts aid in ameliorating the symptoms, they would appear to have a place in the treatment of non-calculous gall bladder disease.

It is not necessary in this discussion to review the various drugs used for symptomatic relief of heartburn, bloating, pain, etc. However, the patient as a whole must be considered comparable to that in any disease. Any underlying psychogenic factor, obesity, endocrine disturbance, or blood dyscrasia should receive proper attention to prevent a functional gall bladder disturbance from progressing into an organic gall bladder disease.

In those patients in whom secondary liver changes have occurred, as demonstrated by bile pigment studies, the modern therapy of liver disease, i. e. increased proteins, carbohydrates, vitamins, etc., must be added to the gall bladder regimen.

SUMMARY

The problems involved in the diagnosis and treatment of the non-calculous gall bladder have been reviewed.

The classification of Russell and his associates has been used as an aid in formulating diagnostic criteria. They have divided gall bladder disorders into the following three main groups:

- I. DISORDERS RESULTING IN DISTURBANCES IN FILLING AND EMPTYING MECHANISM OF GALL BLADDER
- II. DISORDERS RESULTING IN DISTURBANCES IN THE CONCENTRATING FUNCTION OF THE GALL BLADDER
- III. DISORDERS IN BLOOD AND METABOLISM RESULTING IN DISTURBANCES OF THE GALL BLADDER

The history, roentgenogram, duodenal drainage and the study of the bile pigments in the urine have

been evaluated as diagnostic factors. The history and roentgenogram are the two most important means by which the diagnosis is made. However, duodenal drainage is necessary in many cases to determine the presence of stasis and occasionally of the type of infection. The recent conception of regurgitation jaundice and the simplified technics to study bile pigments may be of aid in determining the presence of liver damage.

The place of surgical and medical management in relationship to the type of disturbance has been emphasized.

In the medical management the amount and kind

of fat, the rationale of bile therapy and the consideration of psychogenic and endocrine factors have been mentioned.

The amount of fat used will mainly depend upon its effect on symptoms.

The selection of bile salt therapy depends upon the type of gall bladder derangement. In order to appreciate this, the entero-hepatic bile acid circulation has been described. Oxidized unconjugated bile salts are suggested for flushing. The unoxidized conjugated natural bile salts are recommended for a concentrated bile. Further work is necessary before the last word in bile salt therapy can be stated.

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The Value of a Special Pepsin-Pancreatic Preparation in the Treatment of Peptic Ulcer and Gastric Hyperacidity

By

JONAS WEISSBERG, M.D.

T. H. MCGAVACK, M.D.

and

LINN J. BOYD, M. D.

NEW YORK, N. Y.

TREATMENT OF THE PATIENT with peptic ulcer has always been difficult, because the etiology of the disease is unknown. The rather constant finding of hyperacidity on gastric analysis has resulted in emphasis upon antacid therapy. At best this represents palliative treatment, but usually relieves the pain, the major symptom which makes the patient seek medical aid. Within recent years the efforts of investigators have been directed mainly to discovering an ideal antacid, one which will provide effective and prolonged buffering of gastric acidity. As a consequence, more and more attention has been paid to gastric hyperacidity, earlier emphasized by Palmer as the causative factor in the production of ulcer pain. However, there is good reason to believe that many other things may be concerned in its development, for instance, that it is due to increased gastric tension and motility. It would be fruitless to recount all these, but it is important for us to recognize more than one mechanism in its causation.

Furthermore it should not be forgotten that other organs, such as the gall bladder, pancreas, and colon are related to the phenomenon of epigastric pain. From common experience we know that antacid therapy is therapeutically helpful in various disorders of the abdomen. This certainly cannot stem from a common denominator such as gastric hyperacidity. The reflex effect of disordered gastro-intestinal organs on the stomach is well known. It has been demonstrated in dogs that distending the colon with air or placing croton oil in the gall bladder will reflexly cause increased gastric tension, gastric peristalsis and pylorospasm (7). In man a definite reflex mechanism between colon and stomach has been observed (8), (9). According to Paul (10) epigastric pain due to constipation and so-called "irritable bowel" may occur more frequently than a similar distress due to ulcer. It has been shown that other types of epigastric pain and distress are associated with gastric hypermotility (11), (5), (12), which can be alleviated by the use of atropine.

The definite relationship of the stomach to other abdominal organs raises the possibility that much of

the pain of peptic ulcer may be due to a disturbance in an organ of the gastro-intestinal tract other than the stomach or duodenum. For instance, the pancreas, by virtue of its proximity to the stomach and duodenum, may be profoundly disturbed by a perforating ulcer. This is a grossly obvious cause for altered pancreatic function in peptic ulcer. However, there are certain subtle causes for pancreatic dysfunction in ulcer disease. Thus, the same factor (vagus stimulation, which causes gastric hyperacidity and hypermotility causes stimulation of pancreatic ferments. It is possible that the protracted stimulation which is commonly noted in the ulcer patient may create a state of pancreatic secretory inhibition and exhaustion. The neutralizing effect of gastric acid on the duodenal contents may tend to diminish the effectiveness of the pancreatic ferments. If this happens, faulty digestion may result, secondarily inducing colonic disturbances, gastric hypermotility and epigastric pain. Thus, a vicious cycle is established.

In a study of primary and secondary gastro-intestinal dysfunctions using a special pepsin-pancreatic preparation, McGavack and Klotz (13) and McGavack and Kammandel (14) reported that 60% of the patients with post-prandial abdominal discomfort and pain experienced marked and complete relief. This observation plus the reasonable supposition that the pain of ulcer may be partially attributed to pancreatic dysfunction prompted a study of the effects of a special pepsin-pancreatic digestant in a series of patients with active peptic ulcers.

PROCEDURE

The pepsin-pancreatic tablet (P. P. Tablet*) employed in these investigations has been constructed as a double layered pill. Pepsin, which is readily soluble in the acid medium of the stomach, is present in the outer portion. Pancreatic enzymes and bile salts are present in the inner layer. The latter were protected by a special covering inhibiting their dispersion and solution until exposed to the alkaline ferments of the small intestine. Observations yet to be reported indicate that the dissolution of the inner core of this tablet occurs in

* From the New York Medical College, Metropolitan Hospital Research Unit, Welfare Island, New York 17, N. Y.
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* The contents of this tablet are as follows: pancreatin, triple strength, 100 mg. (equivalent to 1:1 S. P. pancreatin 300 mg.); pepsin U. S. P. 250 mg.; bile salts 150 mg. Cores (a multiple partitioned enteric coating of special type).

the jejunum, usually in the lower reaches and is complete within 3 to 4 1/2 hours.

1. Thirty ambulatory patients with symptomatically active peptic ulcers, in whom the diagnosis was confirmed by X-ray, were selected for the first portion of this study. The patient's symptoms were carefully scrutinized in order to record their nature and severity and to be certain that a true exacerbation of the ulcer syndrome existed. Following the ingestion of an alcohol test meal (50 cc. of 7% alcohol) a fractional gastric analysis was performed in nearly every subject prior to beginning therapy.

In these 30 patients an attempt was made to determine whether the symptoms, particularly pain, could be relieved by a pancreatic enzyme preparation.

They were observed for periods of two to four weeks while taking two P. P. tablets with a little water a half hour after meals. Prior to instituting such treatment, no other medication was given in any instance for at least 10 days and no other forms of medication, such as antispasmodics, sedatives or cathartics, were prescribed during the period of observation. At the end of the first week of this regime the symptomatic response was graded and evaluated in each subject. If the relief was minimal or negligible an additional tablet was administered after each meal. After the second week the response to treatment was again evaluated, and, whenever possible, the fractional gastric analysis, as above described, was repeated.

Patients were allowed to follow previously prescribed dietary regimes, or to eat as they pleased.

2. In order to compare the effectiveness of pancreatic enzyme and antacid therapy in the patient with peptic ulcer above mentioned, 30 patients were given alkalinizing agents in adequate doses for a period of

two weeks. About half the cases received the antacid treatment for two weeks prior to their use of the P. P. tablets. In the other half the order of procedure was reversed. A period of seven to 10 days without therapy was allowed between these regimes in each instance. Evaluation of both types of treatment was made in the same manner. The arbitrary period of two weeks for application of each type of treatment was adopted because it was felt that this was too short a time for the ulcer cycle to complete its course spontaneously.

3. For two weeks fourteen of the 30 patients with peptic ulcer received placebo tablets identical in appearance and taste with the P. P. tablet. The condition of the subject was compared in each instance with his response to the administration of the P. P. tablet.

4. A group of 14 ambulatory patients with gastric hyperacidity but without roentgenological evidence of pathology in the gall bladder or gastro-intestinal tract were placed upon therapy with the pancreatic enzyme mixture. These patients complained of a wide variety of digestive symptoms, such as pyrosis, nausea, epigastric distress after meals, and acid eructations. Arrangement of their regime was similar to that already described for other groups.

RESULTS

1. In our group of 30 ambulatory patients with peptic ulcer, 70% obtained moderate to marked relief of pain with the use of P. P. tablets after meals (Table I.). This response invites the conclusion that the relief of pain must be due to an antacid action. Indeed, there was a mild reduction in the gastric acidity. It was however, not commensurate with the degree of relief of pain, nor did it occur in all patients who were definitely benefited. Composite graphs of

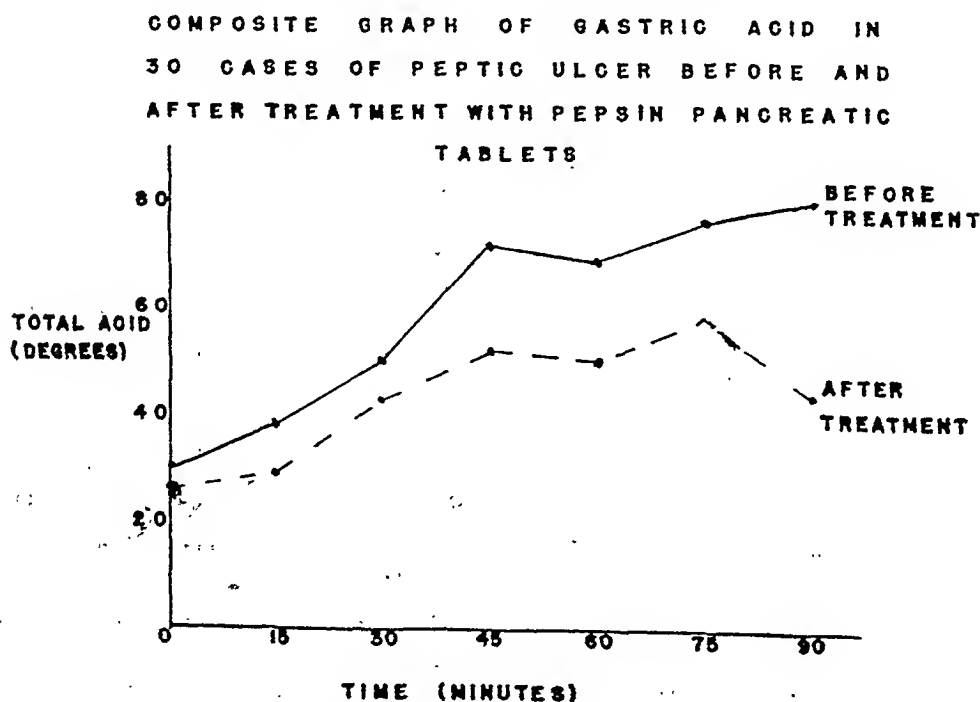


TABLE II
SUMMARY OF CASES WITH PEPTIC ULCER TREATED BY P. P. TABLETS

Case	Age	Sex	Duration of disease	Diagnosis	Major symptoms	Response to therapy*	Remarks
1	22	F	6 wks.	Gastric ulcer	Pain immed. pc; pyrosis, night pain	++	Night pain mod. relieved
2	54	M	10 yrs.	Duod. ulcer recurrent	Pain between meals; nausea; night pain	++	pyrosis ++ relieved Night pain mod. relieved, nausea ++ relieved
3	59	M	20 yrs.	Recurrent duod. ulcer	Pain 2-3 hr. pc; night pain	+++	Marked relief of pain
4	21	M	2 wks.	duod. ulcer	Pain before meals	+++	
5	41	F	3 yrs.	Gastric ulcer	Pain and distress pc.	++	
6	56	M	8 yrs.	Duod. ulcer	Epigastric pain, unrelated to food	0	
7	64	M	15 yrs.	Recurrent duod. ulcer	Pain unrelated to meals; occ. vomit.	+++	Vomiting +++ relieved
8	29	F	2 mos.	Duod. ulcer	Pain 2 hr. pc; nausea; vomit; night pain	0	All symptoms unrelieved
9	61	M	14 yrs.	Duod. ulcer recurrent	RUQ pain before meals; pyrosis	+	Pyrosis + relief
10	31	M	1 yr.	Duod. ulcer	Epig. pain before meals; nausea; night pain	+	Night pain + relief; nausea + relief
11	41	M	3 wks.	Gastric ulcer	Pain soon pc; pyrosis; nausea	+++	Pyrosis and nausea +++ relieved
12	44	F	6 yrs.	Duod. ulcer	Pain before meals; pyrosis, vomiting; night pain	+++	All symptoms +++ relieved
13	50	M	8 yrs.	Duod. ulcer	Pain 2 hr. pc; pyrosis; night pain	+++	All symptoms +++ relieved
14	41	M	4 yrs.	Recurrent duod. ulcer	Pain before meals; nausea	+++	Nausea +++ relieved
15	43	M	3 yrs.	Recurrent duod. ulcer	Pain 2-3 hr. pc; night pain	+	Night pain + relieved
16	32	F	2 mos.	Intractable duod. ulcer	Constant pain; nausea; vomiting; night pain	+	Night pain not relieved nausea and vomiting + relieved
17	38	M	4 yrs.	Duod. ulcer	Pain 2 hr. pc; nausea; melena	+++	Nausea +++ relieved
18	26	M	2 yrs.	Recurrent duod. ulcer	Pain 1-2 hr. pc; pyrosis	+	Pyrosis + relieved
19	40	F	6 mos.	Duod. ulcer	Epig. pain between meals; nausea; vomiting	++	Nausea ++ relief; vomiting + relief
20	51	M	5 yrs.	Recurrent duod. ulcer	Pain 2-3 hr. pc; night pain	+++	Night pain +++ relieved
21	22	F	3 wks.	Duod. ulcer	Intractable pain; nausea	+	Nausea ++ relieved
22	46	M	4 yrs.	Recurrent duod. ulcer	Pain before meals; pyrosis	++	Pyrosis +++ relieved
23	49	M	7 yrs.	Duod. ulcer	sl. hematemesis Pains unrelated to meals; nausea; night pain; vomiting	0	All symptoms unrelieved
24	29	M	1 yr.	Duod. ulcer	Pain before meals; pyrosis	+++	Pyrosis ++ relieved
25	42	F	3 mos.	Duod. ulcer	Pain and vomiting 1 hr. pc;	++	Vomiting ++ relieved
26	54	M	8 yrs.	Duod. ulcer	Pain 2-3 hr. pc; pyrosis; nausea	++	Pyrosis ++ relieved; nausea +++ relieved
27	24	M	3 wks.	Duod. ulcer	Pain before meals; pyrosis	+++	All symptoms +++ relieved
28	38	M	1 yr.	Duod. ulcer	RUQ pain 2 hr. pc; nausea; vomiting	+++	All symptoms +++ relieved
29	45	M	3 yrs.	Duod. ulcer	Peri-umbilical pain unrelated to meals; night pain	+++	Night pain ++ relieved
30	36	F	2 yrs.	Duod. ulcer	Pain 1 hr. pc; pyrosis; melena	++	Night +++ relieved

* Response to therapy is graded as follows:
+++ Marked relief

++ Moderate relief
+ Slight relief
0 No relief

gastric acidity determined before and after therapy are shown in figure 1.

TABLE I

ANALYSIS OF SYMPTOMATIC RELIEF IN PEPTIC ULCER AFTER THERAPY WITH P. P. TABLETS

Symptoms	Incidence (per cent)	Results With P. P. Therapy (per cent)			
		Marked relief	Moderate relief	Minimal relief	No relief
Pain-related to meals	100	43	27	20	10
Night pain	40	42	25	17	17
Nausea	40	50	16	17	17
Pyrosis	37	64	18	18	0
Vomiting	27	37	18	25	25

Of twelve patients with "nocturnal pain," eight were relieved by therapy with P. P. tablets. This would suggest that the pancreatic enzyme preparation had a prolonged buffering action. However, since the contents of the P. P. tablet have very little direct acid neutralizing potentiality, it is more likely that they improved digestion in the small and large bowel and thus decreased gastric tension, with a concomitant inhibition of the production of both acid and pain.

Symptoms commonly associated with the pains of ulcer, such as nausea and pyrosis, were relieved by P. P. tablets in a large percentage of cases (Table I.). Fifty per cent of eight patients were partially or completely relieved of attacks of vomiting.

2. Certain antacids proved slightly more effective than the P. P. tablet in the relief of pain due to peptic ulcer. Antacid therapy in the form of aluminum aminoacetate gave moderate to marked relief to 81% of the patients in contrast to 70% for the P. P. tablets. In several instances the patients were advised to combine the two forms of treatment. These patients reported a preference for the two medications together, because of a seemingly enhanced symptomatic effect.

3. All of 14 patients to whom a placebo was given experienced a return of pain and other symptoms.

4. In the group of patients who presented a variety of epigastric symptoms, and whose only objective finding was gastric hyperacidity, P. P. tablets gave marked relief to 50%, moderate relief to 36%, and only slight relief to 14%, (Table III.). Whether this response represents an effect on the gastric acidity remains problematical, since it cannot be said with certainty that gastric hyperacidity is sufficient to account for the symptoms.

5. During treatment, the possible effects of the P. P. tablets on the lower gastrointestinal tract were sought in each patient. No instances of constipation

TABLE III
RESPONSE TO PANCREATIC ENZYMES OF PATIENTS WITH GASTRIC HYPERACIDITY

Case	Age	Sex	Symptoms	Response*
1	30	M	Pyrosis; dyspepsia pc	+++
2	38	M	Pyrosis; occasional acid eructation	++
3	41	F	Dyspepsia; nausea	+++
4	27	M	Pyrosis; occasional nausea	+++
5	48	F	Dyspepsia immediately after meals; acid eructation	+
6	44	F	Pyrosis; nausea; occasional vomiting	+++
7	51	F	Pyrosis; flatulence; acid eructation	+++
8	36	M	Pyrosis	++
9	28	F	Pyrosis; occasional distress after meals	+++
10	58	M	Intermittent epigastric pain; dyspepsia	++
11	57	M	Pyrosis; slight nausea; sl. epig. distress 1 h pc	+++
12	40	F	Pyrosis; acid eructation belching	++
13	60	F	Vague epigastric distress after meals	+
14	23	F	Pyrosis; occasional acid eructation	+++

* Response to therapy is graded as follows:

+++ Marked relief
++ Moderate relief
+ Slight relief

due to this medication were noted. Indeed, several patients who had previously been constipated found that their bowel habits improved under this therapy. No instances of diarrhea were recorded.

SUMMARY AND CONCLUSIONS

1. A special pancreatic-pepsin preparation (P. P. tablet) was given to each of 30 patients with an active peptic ulcer. A moderate to marked relief of pain occurred in 70% of the cases, which indicates that this form of therapy is rather effective in the treatment of peptic ulcer.

2. Comparison of this form of therapy with an effective antacid revealed that pancreatic-pepsin is only slightly less effective than the antacid.

3. The action of this pancreatic-pepsin is mildly antacid, but inasmuch as nocturnal pain was relieved by its administration, the beneficial effects cannot be wholly explained on such grounds. When all the facts are considered, we believe that pancreatic enzymes promote good intestinal digestion which in turn diminishes gastric tension and secretion.

4. It is recommended that a combination of the P. P. tablet and an antacid be used in the treatment of peptic ulcer.

5. Pancreatic-pepsin therapy proved to be highly effective in the treatment of patients with various upper abdominal symptoms in whom the only objective finding was a gastric hyperacidity.

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Clinical Evaluation of a New Laxative*

By

ALTON D. BLAKE, JR., M.D.

BRYN MAWR, PA.

ALMOST ALWAYS, when the physician prescribes a certain type drug, he is offered a choice. In the case of the laxatives, this opportunity for selection is almost overwhelming. Perhaps it is partly because of their number, plus the tendency to regard laxatives as, at best, homely necessities, that explains why these drugs are seldom subjected to critical appraisal. Yet an agent so widely and frequently used as a laxative seems to warrant careful study, and selection by criteria more exacting than advertising claims. "When the physician is urged to use this agent, he should have available such evidence as will satisfy his questions concerning safety and efficacy" (1).

Definite standards for the "Laboratory and Clinical Appraisal of New Drugs" have been suggested by the A. M. A. Council on Pharmacy and Chemistry (1). The studies of a new laxative reported here were set up along those lines. In the selection of patients, and in judging effectiveness of the product, an attempt was made to apply objective, as well as subjective, criteria. In the clinical toxicity study, detailed laboratory tests were performed by disinterested hospital personnel. Control observations were made whenever possible either by before-and-after-treatment tests, or by comparison with previously used laxatives. The patients were carefully followed throughout treatment, which in most cases extended over several months. Whenever possible, the data collected were subjected to statistical analysis.

The drug investigated was 'Eskalose', a wafer-form bulk laxative employing a new hydrophilic substance, sodium carboxymethylcellulose, as the active component. The chemical itself had been subjected to extensive and thorough experimental investigation, (2) with results that indicated its safety for clinical trial. This colloid appeared, from laboratory data, (3) to have excellent hydrophilic properties and extreme solubility, claimed to minimize the possibility of side reactions such as impaction. Offered in the wafer form, the preparation was suggested as a desirable substitute for hydrophilic granules routinely prescribed in this clinic as part of the regimen for control of functional constipation.

TESTS FOR SAFETY

Twenty-one cooperative subjects were chosen for study. About half the group showed minor gastrointestinal disorders, while the others appeared to have no intestinal abnormality. The diagnoses were confirmed by X-ray and sigmoidoscopic examination.

In complete laboratory examination of these patients before the institution of treatment, results all fell within the normal range. The tests were repeated in 17 patients (four did not return for the final check-up) after four to nine months on 'Eskalose.'

Although these results (see Table I.) showed no deviations that could be considered significant physiologically, as a final check the numerical data from the tests was subjected to statistical analysis (see Table II.).

* This work was initiated with the aid of the John S. Sharpe Research Foundation of The Bryn Mawr Hospital

* Supplied by Smith, Kline and French Laboratories, Philadelphia, Pa.

To our surprise, this showed up three differences that, mathematically, might be considered significant: an increase in the number of red cells per cu. mm., a lesser increase in hemoglobin values, and a slight rise in the blood ascorbic acid. Obviously, these favorable changes must be credited to a general improvement of

the patient's under treatment, rather than to any effect of 'Eskalose.'

Since no unfavorable change of any kind was revealed by either medical or mathematical study of the results, it is concluded that 'Eskalose' has no dele-

Allen P. Shio, Jr., M.D.
Ego, Nara, Pa.

TABLE II
PHYSICAL AND LABORATORY TESTS
RESULTS BEFORE AND AFTER ADMINISTRATION OF 'ESKALOSE'

Case	Age	Sex	Diagnosis	Rectal Exam	Sigmoidoscopic Report	Started on ESC	Finished ESC	Break of ESC	Hemoglobin Gram	Rbc Cells Per Cc. (millions)	Wbc Cells Per Cc. (all types)	% Polymorphonuclear Leukocytes	% Lymphocytes	% Monocytes	% Eosinophils	% Neutrophils	Sedimentation Rate (mm. per hour)	Uric Acid (mg. per 100 cc.)	Urea Clearance %	P.S.P., Test %	Calciferol, %	Total Serum Protein, Gm.	Alb. Phosphatase Sedimentation Unit	Casting Blood Sugar, mg. %	Plasma Ascorbic Acid Upr. %	Prediglycerin Test %	Bromsulphalein 2 cc. (1/2 hr.) test
H.B.	50	F.	Diverticulosis of colon	Diverticulosis of colon	Seattle Sigmoid	Mar. 17 1947	4	13.8	4,310	4150	75	24	1	0	0	12	Normal	71	55	166	83	7.0	4.5	139	0.6	100	Normal
			No Change	Seattle Colon	August 1947		15.2	4,770	5550	58	48	0	2	0	45	Normal	76	55	280	70	7.0	3.0	132	0.7	100	Normal	
F.A.	33	M.	Multiple Polyps of colon	Multiple Polyps of colon	Multiple Polyps	Apr. 14 1947	4	15.7	4,720	2800	75	25	0	0	0	43	Normal	100	85	—	—	6.7	4.3	90	0.3	100	Normal
			Same	Same	Same	August 1947		18.0	4,900	2200	74	28	—	—	—	2	Normal	52	70	—	—	7.0	3.5	97	1.2	—	Normal
H.L.	35	F.	Hemorrhagic Colon	Normal G.I. Tract	Seattle Sigmoid	Apr. 7 1947	4	13.8	4,700	3,400	75	22	3	0	0	15	Normal	100	71	—	—	7.2	7.4	72	1.0	73	Normal
			Same	Same	Seattle Colon	August 1947		13.8	4,200	2,900	64	22	11	3	0	12.0	Normal	85	25+	—	—	6.5	2.6	76	1.0	92	Normal
H.B.	45	M.	Dilatation of colon	Diverticulosis of colon	Normal	Mar. 24 1947	4	15.2	4,670	12,700	58	41	0	1	0	7	Normal	75	50	218	71	6.9	4.4	74	0.3	100	Normal
			No Change	Normal	Normal	August 1947		16.8	4,700	8,700	65	32	0	0	0	10	Normal	61+	70	290	82	6.9	5.1	83	1.0	75	Normal
C.B.	42	F.	Diverticular ulcer	Diverticular ulcer	Normal Sigmoid	Apr. 16 1946	2	12.0	4,020	11,500	71	28	6	0	0	10	Normal	71	25	—	—	—	—	—	—	—	—
			Same	Healed ulcer	Normal Sigmoid	Aug. 20 1947		15.0	4,650	8,500	56	43	4	0	0	12	Normal	20	80	—	—	—	—	—	—	—	—
C.F.	43	F.	Apoptosis of rectum	Normal G.I. Tract	Normal	Nov. 5 1946	6-2	17.8	4,000	8,500	75	24	4	0	0	8	Normal	84	82	250	60	6.5	3.2	64	—	94	Normal
			Same	Same	Same	June 22 1947		15.1	4,650	6,900	74	24	1	4	0	5	Normal	82	65	763	61	6.9	3.0	82	—	100	Normal
C.B.	50	M.	Peptic ulcer	Diverticular ulcer	Normal	Nov. 1946	6-2	19.0	5,000	5,800	76	24	0	0	0	4	Normal	86	—	210	52	5.6	4.1	83	—	100	Normal
			Same	Healed	Normal	June 1947		16.1	5,100	6,500	58	44	1	0	0	5	Normal	78	—	254	54	6.0	4.0	84	—	100	Normal
C.H.	55	M.	Fractured femur	Normal G.I. Tract	Not done	Nov. 1946	6-2	14.1	4,200	5,600	78	22	0	0	0	5	Normal	75	76	—	—	5.5	3.2	81	0.5	100	Normal
			Healed	Normal	Normal	June 1947		15.2	4,800	6,700	75	25	0	0	0	8	Normal	80	80	—	—	6.0	3.0	80	0.4	100	Normal
C.B.	75	F.	Breast cancer	Normal G.I. Tract	Normal Sigmoid	Jan. 1947	6	13.8	4,000	10,500	85	10	5	0	0	12	Normal	—	84	—	—	8.0	2.5	78	0.7	100	Normal
			Same	Normal	Normal	June 1947		13.4	4,700	4,900	88	21	2	1	0	40	Normal	80	80	212	60	6.1	2.8	82	0.3	100	Normal
H.B.	41	F.	Sigmoid Colon	Irritable Colon	Seattle Sigmoid	Feb. 1947	2	18.2	4,900	5,600	71	27	1	1	0	4	Normal	84	100	274	53	6.5	2.6	90	0.4	100	Normal
			Same	Same	Same	July 1947		16.2	5,000	6,400	58	41	1	0	0	5	Normal	100	100	284	56	6.5	2.0	92	0.6	100	Normal
A.H.	59	F.	Sigmoid Colon	Non-functional Gall Bladder	Seattle Sigmoid	Jan. 1947	2	12.0	4,200	5,400	74	28	1	0	0	5	Normal	100	82	—	—	6.3	2.6	96	0.8	100	Normal
			Same	Same	Same	July 1947		15.2	4,600	6,600	72	20	4	3	0	8	Normal	100	76	210	80	6.0	2.0	90	1.0	100	Normal
J.H.	39	F.	Irritable Colon	Normal colon	Seattle Sigmoid	Apr. 15 1947	2	16.0	5,070	4,200	88	32	0	0	0	4	Normal	100	45	294	82	6.7	2.8	80	1.0	100	Normal
			Same	Same	Same	August 1947		16.0	5,400	6,700	70	24	6	0	0	5	Normal	400	70	250	54	5.8	3.0	78	1.0	100	Normal
H.H.	21	F.	Constipation	Normal Colon	Seattle Sigmoid	Mar. 22 1947	2	14.4	4,470	6,000	52	41	5	2	0	40	Normal	83	—	210	60	5.8	3.2	84	0.9	100	Normal
			Same	Same	Same	August 1947		14.1	4,500	5,300	81	34	3	2	0	10	Normal	86	—	220	59	6.2	2.8	83	0.6	100	Normal
H.T.	21	F.	Constipation	Normal Colon	Normal Sigmoid	Apr. 18 1947	2	15.2	4,200	5,700	45	33	16	0	0	8	Normal	100	82	264	45	6.5	3.0	76	0.9	100	Normal
			Same	Same	Normal	August 1947		15.0	4,300	8,700	71	25	1	0	0	13	Normal	400	55	210	53	6.8	3.0	84	0.9	100	Normal
H.A.	35	F.	Irritable Colon	Normal colon	Normal Sigmoid	Jan. 1947	2	12.0	4,000	6,400	82	30	5	3	0	8	Normal	100	85	232	58	5.9	4.2	72	0.3	100	Normal
			Same	Same	Same	August 1947		15.0	4,500	6,800	70	24	6	0	0	5	Normal	95	88	217	62	6.2	4.0	76	0.5	100	Normal
H.V.	42	F.	Irritable Colon	Normal colon	Seattle Sigmoid	Feb. 1947	2	12.9	3,380	6,500	77	49	2	2	0	3	Normal	84	73	—	—	5.5	2.5	84	0.8	100	Normal
			Same	Same	Seattle Sigmoid	July 1947		15.2	4,900	6,200	78	29	4	0	0	5	Normal	100	71	—	—	6.0	2.0	80	0.8	100	Normal
F. B.	45	M.	Irritable Colon	Normal G.I. Tract	Normal	Mar. 17 1947	2	14.8	4,550	7,500	89	46	0	3	0	8	Normal	—	65	—	—	6.1+	4.1	125	0.5	100	Normal
			Same	Same	Normal	July 1947		14.7	4,510	8,800	82	36	2	0	0	5	Normal	—	15	—	—	6.0	2.8	89	1.2	77	Normal

+ Result is questionable, but there was no opportunity to repeat the test.

Use Magnifying Glass if Necessary

TABLE II
STATISTICAL ANALYSIS OF NUMERICAL DATA*

Tests	Average for Group:		Difference Between Averages:		
	Before Treatment	After 'Eskalose' Treatment	Actual Difference	Minimum Significant Difference†	
1 — Hemoglobin — Gm.	14.2	15.1	+ 0.9	± 0.7	
2 — Red Cells per cu. mm. x 10 ³	4387	4716	+ 329.0	± 158.0	
3 — White cells per cu. mm.	7438	7338	— 100.0	± 1180.0	
4 — % Polymorphonuclear Leukocytes	69.4	66.9	— 2.5	± 6.1	
5 — % Lymphocytes	28.1	30.2	+ 2.1	± 5.5	
6 — % Monocytes	1.7	2.8	+ 1.1	± 5.0	
7 — % Eosinophiles	0.8	0.8	0.0	± 1.0	
8 — % Basophiles	0.0	0.0	0.0	—	
9 — Sedimentation Rate — mm./hr.	7.8	8.0	+ 0.2	± 1.2	
10 — Urea Clearance — %	90.2	89.6	— 0.6	± 3.7	
11 — P. S. P. Test — %	76.5	77.7	+ 1.2	± 2.2	
12 — Cholesterol — mg. %	288	274	— 14.0	± 26.0	
13 — % Cholesterol Esters	61.3	61.4	+ 0.1	± 5.1	
14 — Total Serum Protein — Gm. %	6.30	6.39	+ 0.09	± 0.17	
15 — Alk. Phosphatase — Bodansky Units	3.35	3.03	— 0.32	± 0.38	
16 — Fasting Blood Sugar — Gm. %	86.8	86.5	— 0.3	± 3.5	
17 — Plasma Ascorbic Acid — mg. %	0.59	0.80	+ 0.21	± 0.19	
18 — Prothrombin Time — %	97.8	96.3	— 1.5	± 5.8	

* According to methods suggested by R. A. Fisher: statistical Methods for Research Workers, 10th Ed., 1946, Oliver and Boyd, London.

† The significance odds are taken as 1:20, i. e. a probability of 0.05.

terious influence on any of the important bodily functions, and is safe for clinical use.

CLINICAL EFFICACY

Study I: In the hope of obtaining objective data, one experiment with seven subjects was set up on the order of the Gray and Tainter study (4). Three bulk laxatives were compared: a widely used psyllium preparation, a popular tragacanth product, and 'Eskalose.' Stools were collected during three-day control and treatment periods and measured for wet and dry weight, the differences in water volume being used as an index of each laxative's effectiveness.

The general trend of results suggested that 'Eskalose' had a high degree of effectiveness: with this substance, the differences in water retention during control and treatment periods were consistently greater than with the psyllium or tragacanth preparations: the average for 'Eskalose' being about double that for the others. It soon became apparent, however, that daily variations in stool volume of some individuals were extreme, even during the control periods. Analysis of three weeks' investigation indicated that the study must be greatly expanded or prolonged to obtain statistically significant results. The obvious difficulties of obtaining a large number of reliable subjects for several months' study impelled us to continue the investigation along other lines.

Study II: This test employed 35 subjects with a

history of chronic or recurrent constipation. The group was comprised of 22 females and 13 males, ranging in age from 18 to 70 years (median age, 43). Diagnosis showed ulcers in eight, diverticulosis in two, duodenitis in one, multiple polyposis in one; there was no gastrointestinal disease in the remaining 23 subjects.

PREVIOUS LAXATIVE USE

Frequency	Twice daily	2
	Daily	18
	2 to 3 times wk.	4
	1 to 3 times wk.	1
	"Occasionally"	2
Type of Drug	Not stated	8
	Irritant	14
	Emollient	9
	Bulk	15

(Four patients used all three types; three patients used two types)

DOSAGE WITH 'ESKALOSE'

The average dose of 'Eskalose' used initially was two wafers daily, given morning and night. Although in a few cases this dose had to be increased, adequate laxation was usually established on the initial dosage within one to two weeks. However, 12 patients reported satisfactory results within one day; two subjects required a month.

DAILY DOSAGE

NUMBER OF PATIENTS NEEDING:

	1 wafer	2 wafers	1-3 wafers	2-3 wafers	3 wafers
Initial Dosage	0	27	0	2	6
Maintenance Dose	5	28	1	0	1

RESULTS

Results were good in every case according to clinical impression. By subjective comparison with laxatives previously used, results were "as good" or "better," according to the 25 patients reporting. This opinion was given by all the 13 bulk-users reporting and, more surprisingly, by 11 of those accustomed to irritant type-type drugs. All but four of the 35 liked the wafer form.

SIDE REACTIONS

No subjective side reactions were reported through-

out the trial. No evidence of impaction was observed.

SUMMARY AND CONCLUSIONS

1. A new bulk laxative, sodium carboxymethylcellulose ('Eskalose') has been investigated clinically along the lines suggested for the evaluation of new drugs by the A. M. A. Council on Pharmacy and Chemistry.

2. The product appears to have no deleterious effects on important bodily functions, as evidenced by the following tests given before and after its administration: X-ray studies, sigmoidoscopic examinations, complete blood count, sedimentation rate, urinalysis, urea clearance, P. S. P., bromsulphthalein liver test, plasma protein A/G ratio, fasting blood sugar, serum alkaline phosphatase, prothrombin time, vitamin C blood level.

3. The drug is an effective laxative agent, according to objective and subjective tests. The wafer form was approved by all but four of the 35 patients questioned. No side reactions were reported or observed.

4. It is concluded that 'Eskalose' is a safe and effective laxative for clinical use.

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NUTRITION

Nutrition in Geriatrics--Psychological and Somatic Aspects

By

RAPHAEL GINZBERG, M.D.

New York, N. Y.

IT IS GENERALLY RECOGNIZED among physicians who have devoted their interest to geriatrics that nutritional problems of elderly persons are usually more difficult to manage than those of other age groups. (Boas 1, Sebrell 2, Thewlis 3 and others). Since both clinical experience and research have been limited, the individual physician has had practically to pave his own way through vague and difficult conditions. Unknown pathophysiological processes in senescence and psychological reactions of different kinds have been the main obstacles to discovery of the real causes

of existing disturbances.

Among the psychological factors which hinder to a great extent the recognition of nutritional difficulties in the so-called normal aged is the whole atmosphere in which elderly people live. This atmosphere does not encourage the application of new approaches to their problems. Who really believes that there is any essential help possible for elderly individuals? Nor does the elderly person himself expect too much from medicine and science. His normal reaction therefore is to oppose and resist innovations. In the opinion of the elderly person himself, the old must suffer, and he is supported in this belief by other members of

his family, especially those of the younger age groups. The elderly person is afraid that experimentation will aggravate rather than improve his condition.

Senectus ipsa morbus — this is the belief of the great majority; only a few are convinced that *morbus* is as accidental in senescence as it is in other age groups. Nutritional disturbances in the aged can be avoided as well as can other disturbances. We need, however, more knowledge of and further search into the problem.

Through the ages only single physicians have devoted themselves to study of the nutritional problems of the aged.

Galen said: "*Plures gula quam gladius occidit*" — more are killed by gluttony than by the sword. Hufeland (4) wrote: "The first thing which, in regard to diet, can act as a shortener of life, is immoderation . . . To eat too much means when people eat till they can eat no longer and the following are the signs: when one experiences a heaviness and fullness of the stomach, yawning, belching, drowsiness, and confusion in the head. The old rule, which contains much truth, ought therefore to be always observed: Give over eating while you have still appetite left."

Today we recommend moderation, as did Hufeland 150 years ago, because "old people show changes in the salivary, gastric and pancreatic secretions (except amylase) all of which are a decrease in the quantity of secretion and enzymes" (5). We cannot therefore expect that in cases of immoderation and overeating food will be properly digested.

Among elderly patients, of course, there are several types. One group of the aged cannot stop eating and is gluttonous; a second group appears to consist of nutritionally well balanced people who eat very moderately; a third group suffers from lack of appetite — members of this group are often afraid to eat and develop strange habits as they become older; they have a faulty diet and are under- rather than overfed.

It is, however, not accidental that Hufeland mentioned moderation as the most important aspect of the dietary problems of elderly people. It is a fact that elderly individuals, especially those in their sixties and seventies, suffer from too good rather than impaired appetite, although "indigestion" and other gastrointestinal troubles, such as constipation, diarrhea, belching, heaviness, abdominal pain and flatulence, occur more often among the aged than among members of other age groups.

In younger age groups we find a relationship between appetite and gastric secretion. Hypo- or achlorhydria is usually accompanied by impaired appetite; normo- or hyper-acidity goes with a good or even excellent appetite. Not so in elderly persons. In a group of 51 persons between the ages of 75 and 102, Sokolinsky (6) found good or satisfactory appetite in 49, although hypo- or achlorhydria existed in 43 cases. In only two cases was appetite either absent or poor.

The latter, however, did not have achlorhydria.

It is quite possible that the Ewald test does not furnish an exact picture of gastric chemistry in elderly people. The psychological response of elderly patients to the whole procedure of an Ewald test certainly is entirely different from their reaction to a normal food intake, especially to the foodstuffs to which an elderly individual is accustomed. It will be necessary in future investigations to take these and other factors into consideration. It seems to be clear, however, that diminished gastric and perhaps salivary, hepatic and pancreatic secretion does not greatly affect the appetite of elderly individuals.

In the very complicated mechanism of appetite psychology is as much involved as is pathology or physiology. Appetite is not only a signal that the organism needs food, it is not only an expression of the expectancy of enjoying a meal; it is also a psychological reaction to environmental conditions. We do not always get the food we like, and even when hungry must wait until circumstances allow us to eat. Excitement, worry and other factors affect our appetite. The desire to eat may become subordinated to neurotic reactions. Such reactions develop early. They are plainly observable in childhood and often persist into adolescence and beyond. Although these mechanisms are not so apparent in the middle-aged groups, they are reactivated in the aged, especially among persons who are dependent either upon relatives with whom they live or on institutions in which they expect to be confined for the rest of their lives. Viewed psychologically, an impairment of appetite is often an expression of opposition and protest against conditions which a person finds unacceptable and is directed both against his environment and himself. The psychological content of these reactions among the aged differs, of course, greatly from that of the younger age groups.

Another psychological or psychosomatic factor is important in considering the dietary problems of elderly people. An aged person is conservative in his choice of food. He prefers foods to which he is accustomed. He enjoys this kind of food and digests it better than he does other foods. Habits play a very important role in the life of an elderly person and especially so in his digestive processes.

In the parlance of science, habits are nothing more than conditional reflexes, or, better, a network of reflexes to which, voluntarily or involuntarily, consciously or subconsciously, a person has been conditioned throughout his whole life.

The importance of food habits in elderly patients was recognized a long time ago. For example, Day (7), in a book published a century ago, wrote: "Regular habits of life are essential to the wellbeing of old people . . . I will even go so far as to assert that in many cases it is dangerous to attempt correct habits which have an acknowledged pernicious effect." Whether we would go so far today is questionable.

But it is obvious that Day attached great importance to the habit factor in elderly people. In the course of the decades this point of view has been forgotten and has only recently — since geriatrics became a new branch of medicine — been rediscovered.

Modern experts in geriatrics again stress the necessity, in working out diets for elderly people, of taking very seriously the matter of the habits and customs of elderly people.

Meyer (8) states that in general it is recommended that the diet of the aged should not be drastically changed from their normal habits and customs.

Thewlis (3) emphasizes: "The food, whether at home or in a hospital, should be that to which the patient has been accustomed and not that which the nurse thinks most suitable" (p. 116). At home, of course, this might be managed, but it is another question whether the aged patient can get an appropriate diet in a hospital, even in the best one.

A patient's habits can become harmful to him. A faulty diet and improper nutrition, an insufficient amount of proteins and vitamins may through the years, and even months, produce cumulative effects (2). Somatic changes and pathological processes may impel the physician to eliminate from or add to the patient's diet this or that food item, but the habits of the patient must be the point of the physician's orientation. The solution must be found in close cooperation between physician and patient. Arriving at a compromise that is acceptable to both patient and physician is the first step on the way to possible success.

Food habits have deep ethnographical roots. The customs of the country or province where the patient was brought up often determine his habits for the rest of his life. A routine convalescent diet illustrates to a certain extent the origin of the food habits of elderly persons. A convalescent diet which consists of so-called easily digestible foods is the pattern of the menu of the aged. Laymen and physicians in each particular country are usually in agreement about the expediency of a convalescent diet. How different, however, are these diets in different countries!

In Russia, for example, and especially in the western provinces with a once considerable Jewish population, chicken, and chicken soup with a high fat content, were considered as most desirable foods for a sick or convalescing individual. Amazingly enough, the patients usually tolerated this heavy food well. To give the same or a similar diet to a Frenchman really would be catastrophic. For the Frenchman's convalescence there must be provided "bouillon de legumes" which has been cooked for hours, as is common in France. It would be a grievous error, however, to suggest the same vegetable soup to a Russian, German or American. In Russia and Germany the preferred meat for a light diet is veal. Not so in America. Lamb chops and steak would be more acceptable in this country and in France. Lamb is, however, disliked in Austria and parts of Germany. Schlesinger (9),

for example, suggested serving elderly people lean beef, veal, chicken and squab. He warns, however, against duck and goose, which is perfectly correct, and — against lamb. In France, horse meat is considered a food of high nutritional value and is often prescribed for convalescent patients. I hardly think that any physician in this country would dare to prescribe horse meat.

A very interesting item in diet is milk. It is unnecessary to stress that in this country milk is considered an essential food for young and old, and the question is not as to quality but only as to quantity. In this country one may hold the same opinion as Thewlis (3) (p. 130) and recommend at least one pint a day, or one may agree with others and suggest more. Not so in Britain. Todd (10), a contemporary British physician and geriatrist, in his recent book, stated (p. 46): "Milk is ideal for the healthy youth . . . We (elderly) do not need the substances in milk."

Another British physician, Hutchison (11), suggested, for example, a little whisky and water with a biscuit at bedtime. Presumably many aged persons in Britain will accept and perhaps enjoy this little drink of whisky and water at bedtime. It is inconceivable, however, to think of a Russian enjoying such a supper.

Certainly prejudice and misinterpretation are sometimes responsible for food habits. Habits, however, are often an expression of common-sense judgment and a reaction to conditions peculiar to a given country.

But in addition to habits of ethnographical origin, every family and every individual develops its own habits. Some people like their food hot, others like it lukewarm. Some aged people can tolerate rye bread but do not digest whole wheat bread. If one is not accustomed to toast, there is no point in insisting upon his eating it. Some people prefer sweet, others plain potatoes. If an aged individual likes one kind of carbohydrates, it is inexpedient to shift to another. Cabbage is certainly a "heavy" vegetable. If, however, the aged person has been accustomed to this vegetable, he should have it, prepared in the style that suits him. Unless changes are definitely indicated they should be avoided as far as possible.

At first glance an individualized approach to nutritional problems in old age seems rather to complicate the situation. One must, however, bear in mind that little is known about the pathophysiology of the gastrointestinal tract of the aged. The physician is compelled in each individual case to work through the difficulties manifesting themselves as a mixture of somatic and psychological conditions. Consequently the range of possible mistakes is great. The number of errors can only be diminished by creating a better relationship with the patient. Close cooperation with him is of utmost importance.

To achieve this relationship, however, is not easy. The elderly patient is usually on the defensive against his environment. Stubbornness, resistance, mistrust,

annoyance, desperation are often his reactions. Since the elderly person is much less flexible than members of other age groups, skill and patience are necessary in order to penetrate the psychological wall.

A serious discussion of the patient's habits can do more than anything else to open the way to a better understanding. After overcoming the psychological difficulties, one must always search for possible organic causes underlying the patient's condition.

In these days of overemphasis on psychology one runs into the danger of satisfying oneself with psychological explanations of various symptoms. Psychological explanations may be misleading. Overlooking of the somatic part of the existing troubles is quite possible. Let us consider the following: It is well known that elderly people, or at least a considerable part of them, try to avoid meat in their diets. From the medical angle this would not always appear to be expedient. Low plasma proteins, microcytic anemias and similar conditions which are not uncommon in elderly people can to a certain extent be corrected by an increase in meat intake. Indeed, the results of recent experiments indicate that elderly people need more protein than do persons in the younger age groups. Kountz, Hofstatter and Ackermann (12), investigating nitrogen balance in elderly people, found that a majority of their cases who were put on a "balanced diet" showed a negative nitrogen balance. They found that in order to save the elderly patient from a steady nitrogen loss, protein in the diet must be substantially increased. These and other observations make it obvious that the fear that meat can harm elderly patients is unwarranted.

Our elderly patients, however, do not think so. Their arguments, at least in part, may be traced to views of medicine which were popular many decades ago. The elderly person who is afraid of arteriosclerosis or possible kidney damage adheres to a theory of former times which has long since been relinquished. If one talks, however, of general deterioration as a result of meat intake and becomes involved in a quarrel with wellwishing relatives concerning the usefulness of meat in the diet, then the matter takes on psychogenic, or even psychotic, features.

It would be erroneous, however, to believe that one has solved the problem when the psychological or psychiatric phases have been eliminated. All that is known today concerning gastric secretion, which is primarily responsible for protein digestion, leads one to anticipate that gastric secretion is definitely diminished in the great majority of those of advanced age. If this factor is not considered one may overlook a major cause of what appears at first glance to be a psychogenic reaction. These cases furnish an example of a psychosomatic condition in which psychogenic reactions grow up around a somatic basis. Theories, explanations, superstition and other psychological factors are indeed secondary to the facts of hyposecretion, achlorhydria, and so forth. These gastric conditions provoke the so-called indigestions from

which elderly people suffer. The patients, however, are not aware that their "indigestion" is connected with difficulties in protein digestion. Often they do not even mention this "indigestion" because these manifestations are considered as normal and natural in old age. Sometimes elderly people are afraid that minor complaints may lead to interference with their diet, and deprive them of foods that they like. Sometimes the situation is even more complicated.

All these feelings and thoughts are consciously or subconsciously suppressed and, after taking a psychological detour, are to a certain degree correctly ascribed to meat. Despite the misleading fireworks of psychogenic reactions the patient guides the physician to the real organic source of the difficulties.

Diminished gastric secretion in the aged was described by Dedichen (13), Osterberg, Vanzant, Alvarez and Rivers (14), Sokolinsky (6), Meyer and Necheles (5), Meyer, Spier and Neuwelt (15), Bloomfield (16), Meyer (8), Freeman (17), Rafsky and Weingarten (18), and others. One cannot, however, assert that the question has been solved. For example, the majority of investigators have established that secretion of hydrochloric acid and pepsin is impaired, yet in all of Sokolinsky's cases diminished hydrochloric acid secretion alone was found, and in none of these was secretion of pepsin disturbed. On the other hand, Rafsky and Weingarten (18) stress that hyperchlorhydria was found in 12.7 per cent of their subjects. Of course, the number of cases investigated is not ample to justify any definite conclusions. The laboratory data, however, confirm the clinical impression that in elderly persons one must deal with at least two, or perhaps three, types of gastrointestinal chemistry.

Two of these types are definitely antipodal. One develops hyperacidity, the other hypo- or anacidity, with or without diminished pepsin production. The older the people become, the more prevalent the hypo- or anacid type. A considerable number of the hyperacid type are found among sixty and seventy-year-olds, but among those ninety years old and older, the type becomes a vanishing minority.

In addition to the described symptoms, the two antipodal types have other obvious characteristic features. Therefore it may be assumed that constitutional factors are involved in gastrointestinal processes. When Hufeland suggested moderation in food intake he probably had in mind the short, overfed elderly person who always has a good appetite and relishes his meals. They do not know when to stop eating, and realize only after a meal that they have had more than enough. Sometimes they complain of heartburn; they tend to be constipated. Their weight is their tragedy. Talk about diet irritates them or induces a depressive reaction. From their physician they expect tablets or pills, but not talks about moderation. Hyperazotemia, high blood pressure, hypercholesterinemia and similar conditions are rather common among them. Psychologically they belong to the group which manifests the cyclic temperament. They can

be gay, jovial, hypomanic, and sad, depressed and hopeless as well.

Elderly persons with hypo- or anacidity differ entirely from the group just described. Psychologically they are more complicated. Somatically they are slender and under- rather than overfed. They are dissatisfied, easily offended, easily irritated and less co-operative. They do not suffer from the results of immoderation at all; on the contrary, they are rather inclined to eat less than necessary. They prefer carbohydrates to meat. They are often considered weak, but their resistance is usually much better than that of the stout and overfed. Hypoproteinemia, rather than hyperazotemia is typical of this group. Observing these patients clarifies the animal experiments which have proved that a certain type of starvation does not shorten but rather prolongs life. (See Riesen. Herbot, Walliker and Elvehjem (19); Carlson and Hoelzel (20); Lansing (21). The majority of elderly persons over eighty fall within the second type described. A slender person does not become stout in old age. A stout person, however, if he survives, may become slender under the influence of unknown degenerative processes through his eighties or nineties.

These and other clinical experiences have up to now not been studied by laboratory and other investigations. If confirmed, these observations may lead to new ways of solving nutritional problems of the aged. It seems already to have been proven that the diet of elderly persons may include substantial amounts of proteins. Persons with hypoacidity will accept proteins if their digestion of protein can be improved. In such cases hydrochloric acid and pepsin must be used liberally.

It is unnecessary to stress that we must be sure that no impairment of kidney functions is present. Shock (31) has pointed out that the excretory capacity of the kidneys may be diminished in so-called normal old people. Before prescribing greater amounts of protein, one must be sure that no increase of creatine and non-protein nitrogen will occur in the blood. Aside from this there appears to be no contra-indication. We must, however, bear in mind that our knowledge of the elderly organism is limited. The elderly patient must be closely observed and the physician must be on the alert.

Is fat essential in the diet of elderly persons? From the point of view of possible arteriosclerotic processes it is preferable to avoid fat. Very often a high caloric diet seems to be indicated for slender and under-nourished individuals. Should one prescribe a fat-rich diet in these cases?

Physicians interested in nutritional problems of the aged have felt for a long time that elderly persons should use fat with care. Day (7), in 1849, wrote: "The cream or butter is the only constituent of milk that is likely to disturb the stomach . . . The oily fishes, as eels, herring, salmon, etc., should be avoided . . . Rich puddings and every form of pastry should be carefully avoided . . . I need hardly enter a protest against that insidious poison, the *pâté de foie gras*."

Schlesinger (9) mentioned that rich food provokes long lasting diarrheas in elderly individuals, and recommended a diet with a moderate fat content. Thewlis (3) felt that we suffer from an excess of fat in our diet. In his opinion many persons in the older age groups can well afford to do with much less fat than they receive. Todd (10) relates: "Those of us who went to Switzerland and took out the hotel picnic lunches often will remember how the hard boiled eggs which were always present became somewhat of a problem after the first week or so; the eggs became repulsive to many of us. This is because the egg yolk contains much fat and lipoid substances . . ." Todd advocates a low fat diet for elderly persons. Meyer (8), Freeman (17) and several others are of the same general opinion.

Recent studies of the liver, gallbladder and pancreas suggest that these organs show much more damage by the time old age occurs than may have been expected. Rafsky and Newman (22) believe that liver impairment in the aged is probably a normal condition. In another paper (23) they emphasize that abnormalities in liver function as revealed by tests are found in apparently healthy persons above sixty years of age.

Rosenthal's (24) reports on autopsies revealed the largest percentage of gallbladder diseases in persons who had reached their seventh decade. Among his group, 65 per cent of the females showed various forms of gallbladder abnormalities. In his series of 78 autopsies of patients with cholelithiasis, 67 per cent had shown no clinical symptoms, and 15 per cent had only vague abdominal complaints. His cases of gallbladder disease showed a high percentage of liver damage. In his opinion gallbladder diseases are frequently demonstrated in autopsies of elderly patients.

Andrew (25), who studied changes in the pancreas of rats and men, writes that his findings "indicate that in the pancreas of both rat and man there are certain changes so definitely connected with the aging process that they may be called 'senile' changes. The extent of these processes is in many instances so great that very large portions of lobules, or even entire lobules, become converted into cavities. These changes appear to be indicative of decreased function of the exocrine portion of the gland in old age." Niles and Martin (26) state that a deficiency of pancreatic secretion may be expected to appear frequently in patients past forty.

Liver and pancreatic diseases are very difficult to recognize in any age group and especially in the elderly. Here one deals not only with acute processes but with sequelae of (1) previous infections or intoxications; (2) arteriosclerosis and other vascular diseases; and (3) involutional changes.

Recent experience has shown how easily pathological liver conditions can be overlooked. Capps, Shorov and Barker (27), reporting their experiences based on the observation of approximately 8,000 cases of in-

fectious hepatitis, of which 2,000 were systematically studied, and the appropriate literature surveyed, arrive at the following conclusion: "Prior to the war the clinical picture of hepatic disease except in its severer forms was vague and incomplete. The symptomatology of the nonicteric forms of hepatitis was almost unknown and seldom recognized."

It is to be anticipated that a majority of people will bring with them into their senescence a damaged liver. They grew up in a time in which the diagnosis of hepatic disturbances was poorly developed. The possibility of existing or persisting liver damage in those of advanced age is very great. In doubtful cases it is probably less erroneous to consider a possible liver-gallbladder-pancreas damage than to satisfy ourselves with diagnoses of arteriosclerosis, indigestion, and so forth.

Apparently the best thing to do for these conditions is to eliminate fat from the diet entirely. This may be prescribed for a short or a long period of time, or even permanently. As a source of caloric supply fat can be replaced by carbohydrates. Vitamin A can be supplied by green and yellow vegetables. If necessary, Vitamin D may be given by capsule.

Fat does not appear to be essential to the proper nutrition of elderly patients. Todd states definitely (p. 25) that "Fats are probably not essential with the exception of some which may act rather as vitamins..."

While some of the properties of fat are as yet not recognized, a temporary or permanent elimination of fat from the diet of elderly persons can do no harm. After a period of no-fat, one can always try a low-fat diet. A no-fat or, if tolerated, a low-fat diet, is the diet of choice among elderly people. Bile salts and pancreatic preparations may be used in order to improve the fat digestion.

Carbohydrates are unanimously recognized as the most easily digestible food for elderly persons. On this matter physicians and laymen are in complete agreement. Elderly individuals usually prefer carbohydrates.

According to Meyer and Necheles (5) the conversion of carbohydrates by salivary amylase to maltose and dextrose is markedly depressed in the aged. Carbohydrate digestion is probably completed by the pancreatic amylase.

Carbohydrates are a main food in aged persons. If, however, the pancreas, and especially its insular part, is damaged, a diabetes can easily occur. Since a diabetes, especially in mild form, may not be readily detected, frequent determination of blood sugar is highly desirable. It often happens in the case of elderly persons that in the course of a routine check-up the presence of a mild diabetes is discovered. Once recognized, the condition is usually easily corrected.

The intake of carbohydrates in obese people must be regulated.

One must, however, consider the matter of digestibility of cellulose in elderly persons. The importance

of fruit and vegetables in the diet has long been recognized. Fruits and vegetables, however, consist to a considerable degree of hard-to-digest cellulose, and flatulence has been traced to the eating of heavy vegetables and fruits. In ancient times physicians were greatly concerned as to the means of solving this dietary problem. Day (7) recommended avoidance of peas, beans and the cabbage tribe. Cucumbers, in his opinion, were to be strictly avoided.

The modern physician holds virtually the same belief (26). The main cause of gas formation in elderly people, they claim, is impairment of cellulose digestion. Since cellulose is affected by bacterial action in the intestinal tract, colon bacilli must be held responsible for these disturbances.

Why colon bacilli work unsatisfactorily in elderly persons is obscure. It has not even been established whether they alone are responsible for the difficulties in digestion of fruits and vegetables. There is wide variation in individual tolerance of these nutritionally important foods. Often it is not so much the particular vegetable or fruit, but the quality, that is responsible for intestinal troubles. Soft, ripe and palatable fruits, and fruits to which the patient is accustomed, usually are tolerated well.

It is a matter of fact that typical or atypical vitamin deficiencies of subdeficiencies are extremely frequent among geriatric patients. Whether a diminished intake, absorption, or impaired utilization is mainly responsible for vitamin deficiencies remains undetermined.

Recent laboratory evidence indicates that vitamin balance in elderly persons is definitely and sometimes highly disturbed. An almost complete list of published articles on this subject has been compiled by Freeman (17), Rafsky and Newman (28), who have done a great deal of vitamin research, and have recently summarized their experience.

It seems established that so-called normal aged persons have subnormal amounts of carotene and Vitamin A. Kirchmann (29) found a normal ascorbic acid blood level in only one of her elderly patients, and this was an individual who had been living on an exclusively vegetarian diet. Kirchmann and others have shown that in elderly people both a low cevitamic acid blood level and a high Vitamin C tolerance are present. There is a definite tendency toward low blood levels and low elimination of Vitamin B-1. Rafsky and Newman (22) found that nicotinic acid can cure porphyrinuria in elderly people. In these cases the liver function impairment which led to porphyrinuria may be caused by nicotinic acid deficiency. Clinically, cheilosis, irritation of the skin, changes in the tongue and many other symptoms ascribed to vitamin deficiency are often seen in elderly people. The administration of large amounts of vitamins, especially in combination with liver preparations, not infrequently has produced striking improvement of the symptoms as well as in reducing fatigue and sometimes even mental

depression. It is generally agreed that much larger amounts of vitamins must be administered than has been the case up to now.

Since gastrointestinal absorption may be disturbed, vitamins must be administered orally and parenterally. After a period of injections, one may shift to oral doses and vice versa, or simultaneous oral and parenteral use of vitamins. Results can not be expected within a short time. Resistance and disappointment on the part of the patient, and especially on the part of the patient's relatives, can interfere seriously with the therapy and constitute the main obstacle to therapeutic success.

CONCLUSIONS

Nutrition in geriatrics is a difficult problem for both patient and physician. Elderly persons seldom have an appropriate and beneficial diet. They either eat too much and are obese, or they receive less food than necessary and are undernourished. Belching, flatulence, constipation and diarrhea are often events in the life of the so-called normal aged.

Two constitutional types among the aged and their psychosomatic reactions have been described. It was shown that the psychological atmosphere in which an elderly person lives does not differ very much from the atmosphere that has been in existence for hundreds of years. Prominent physicians in the first part of the nineteenth century, for example, were convinced that physiology and pathology in old age were identical (30). An attitude of pessimism and desperation has been typical for centuries and has not changed very much in our times. A small group of physicians and social workers are endeavoring to alter this traditional attitude of hopelessness which bars any constructive approach to geriatric problems. Their ideas, however, now are beginning to penetrate very slowly into the minds of the present generation.

The elderly person lives in an environment which does not evince too much interest in or understanding of him and his difficulties. The approach to an elderly person which views him as an infirm, helpless and incapable individual is outdated. The point of view that an elderly person must suffer because he is old is no longer justified. One should no longer diagnose the illness of an aged person suffering from gastrointestinal disturbances as senescence. Rather the patient's condition should be thoroughly analyzed to ascertain the character of the disturbance and the patient treated by means of appropriate diet and medication, as is done in other age groups.

It must be borne in mind that there is disturbance in digestion of proteins in a considerable number of

elderly people and that this disturbance is the result of a diminished secretion of hydrochloric acid. This condition can be easily corrected by proper diet and the administering of hydrochloric acid and pepsin. If hyperacidity is present, which is rarely the case with elderly persons, especially in those over eighty, these cases must be handled accordingly.

It has been mentioned that we must be especially careful as to fat intake of elderly persons. Fat can be entirely eliminated from the diet without causing any harm to an aged individual provided a necessary supply of fat soluble vitamins is taken. Biliary salts and pancreatic substances are often of significance in the treatment of certain conditions.

Although digestion of carbohydrates in the aged is rarely disturbed, the use of diastase has proved useful.

Vitamin deficiencies in advanced age can be improved and even cured by oral and parenteral administration of vitamins.

The standard diet of elderly persons must be based on (1) high carbohydrate intake (with diastase if necessary); (2) high protein intake (with hydrochloric acid and pepsin if necessary); (3) low or no fat intake (with pancreatic substances and biliary salts if necessary); (4) supplementary administration of large amounts of vitamins, orally and parenterally.

The diet of the elderly person must be highly individualized and adapted to his habits and customs.

The influence of psychological factors has been discussed, as has the importance of such phenomena as habits. It has been stressed that a sound psychotherapeutic approach is possible only if real organic troubles are recognized. Such recognition will create the basis for real cooperation between patient and physician which is necessary in the treatment of persons of advanced age.

At first glance nutrition appears to be only a part of gastrointestinal problems, but actually the solution of the nutritional difficulties of the elderly individual is much more complicated. Psychology and environmental factors are as much involved as is pathophysiology. The more adequate the psychological condition, the better the digestion and the more favorable the response to medication if any is used.

The new approach must be based on the recognition that an elderly individual should be active for as long as possible, that he must be considered as a valuable member of society, and that he must have his place in our life and feel that he is not a burden either to himself or the community.

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Nutrition Notes

Achlorhydria in Pernicious Anemia


As far back as 1927, Cornell (1) stated that "If one fact has received ample confirmation in connection with the entire subject of pernicious anemia, it is this: 'The stomach contents almost never contain free hydrochloric acid.'" Levine and Ladd (2) in a series of 150 cases by the use of the fractional meal found achlorhydria in 99 per cent. Faber and Gram (3) in 54 cases studied between 1907 and 1922, found achlorhydria in fifty. Panton et al. (4) reported achlorhydria in all of 117 cases of pernicious anemia. Percy (5) found free HCL in but one of 129 cases. In 1946 Russell Haden (6) made the dogmatic statement: "No patient with idiopathic pernicious anemia has free hydrochloric acid in the gastric contents." However, it seems unlikely that the argument can yet be considered closed.

Very recently Murphy (7) believes that he has submitted satisfactory evidence to prove, contrary to accepted belief, that pernicious anemia does exist in association with free hydrochloric acid in the gastric secretion and therefore that achlorhydria is not essential to the development of true pernicious anemia. His case is well worked up, and, after reading his detailed description, it may seem necessary to accept his claim. The absence of intrinsic factor in the patient's gastric juice was well established, nevertheless the patient showed a hyperchlorhydria on fractional test meals. The marrow biopsy did not reveal a megaloblastic marrow

picture but the author argues this was because the biopsy was not made prior to specific therapy. The blood smears were characteristic of the Addisonian disease however. Differential diagnosis from other forms of macrocytic anemia was satisfactory. The patient recovered on refined liver extract. He feels that his case supports Morrison's theory of dissociated dual function of the oxyntic cells of the gastric mucosa, explaining why a cell could continue secreting acid but without the intrinsic factor. At least, Murphy has made an excellent beginning of a crusade against the very old and very ironclad theory that achlorhydria invariably accompanies pernicious anemia. Although it is becoming difficult to find untreated cases today (partly because most patients with any kind of anemia receive pharmaceutical preparations containing at least some liver extract in addition to iron, folic acid and vitamin B) we hope that many others will follow Murphy's meticulous methods in a search for further cases like his which seem to deny an ancient and accepted rule. One frequently has the feeling that there may be more than one kind of true pernicious anemia: Murphy's case may be one of a minority group. His work, taken together with the accumulating data on folic acid and the isolation of vitamin B₁₂, seems to promise us a clearer understanding of pernicious anemia within the next few years. It will be particularly gratifying if light can be cast upon the so-called achrestic anemias.

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Early Vitamin-Deficiency States

Pre-clinical vitamin deficiency states have probably been a dream of every creative internist for the past two decades, for such states ought logically to exist and should explain many vague physiological conditions which now are nameless or given such generic titles as psychoneurosis, fatigue, nervous exhaustion, and so forth. However, the barrier to making such a dream come true consists of difficulty in recognizing such physiological states as specific vitamin deficiencies. Is it not true that in clinical practice actual objective signs of specific deficiencies are somewhat uncommon? It is becoming recognized that human beings usually suffer from multiple rather than single deficiencies. Such signs as rickets, cheilosis, glossitis and xerophthalmia are becoming scarcer in American society. Generally speaking, only experimental animals enjoy the questionable distinction of suffering from highly specific, single nutritional deficiencies.

To go back a step further and attempt to diagnose specific vitamin deficiencies in human beings before objective signs have developed, requires routine examination of urine and blood serum for their vitamin content. Vitamin metabolism with its complicated, and still frequently controversial methods of examination, usually lie beyond the scope of practical internal medicine. As a result, the easiest solution of the difficulty is to prescribe multiple vitamin preparations in therapeutic doses where suspicion of multiple deficiency exists.

Primary deficiency states are due to inadequate diet and are seldom seen in the U. S. A. or England today. In *secondary deficiency states*, the diet is adequate, but there is interference with ingestion, absorption or utilization of vitamins or there are increased bodily requirements due to exertion or infection. Leitner* has suggested that large doses of one purified vitamin (i. e. one single enzyme system) may easily upset the

balance in deficiency states or may inhibit other enzyme groups which at that moment are present in abnormally low amounts.

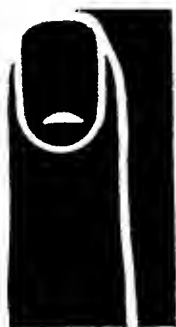
No doubt, this problem of early vitamin deficiency states is related rather closely with protein nutrition, and the efficiency and health of the liver particularly. Probably the use of heavy dosage of vitamin B complex and especially its various factors, may at times do some harm. Potent liver extract is a good stabilizer when doubt exists as to the balance of vitamin enzyme systems in a given case, provided the patient does not have polycythemia. The profession now is on guard with respect to over dosage with vitamin D. Several of our leading nutritionists do not personally use vitamin preparations on themselves, preferring to rely on a well-balanced diet.

There is a trend away from vitamins toward proteins. There is, fortunately, a tendency today to envisage the diet of a patient as a whole and an increasing care in emphasizing his caloric needs as well. We cannot always detect early vitamin-deficiency states but we should be able to recognize starvation in the undernourished and discover why, in the United States of America, today anyone should starve or be starved.

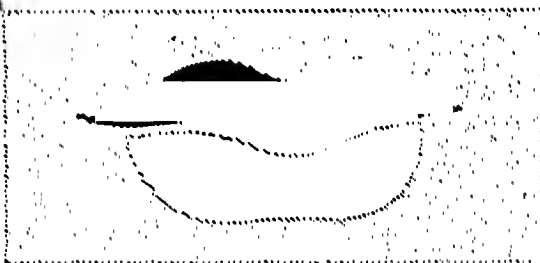
The Effective Factor of Liver in Pernicious Anemia

Castle et al. (1) concluded in 1944 that it is reasonable to continue to regard the "extrinsic factor" as a thermo-stable component of the vitamin B complex as yet unidentified. Clark (2) found that U. S. P. crude and refined liver extracts both contain vitamin B factors and that the refined preparations contain as much or more riboflavin, niacin, pantothenic acid and vitamin B₆ (folic acid) than do the crude preparations, but he could not see any evidence to date (1945) that any one of the well-recognized B factors is directly involved in hematopoiesis in pernicious anemia. The work of Spies and his co-workers (3) showed that folic acid caused blood regeneration in macrocytic anemias including pernicious anemia but later work has shown that while this is true, folic acid has no effect on the neurological phases of Addisonian anemia. It was considered by many that the factor in liver which produces normal marrow activity in pernicious anemia might be different from the factor in liver which exerts an arresting action on the neurological lesions. However, we now have what appears to be positive evidence that one single factor produces both effects and that this single factor has been isolated in pure crystalline form. Rickes et al. (4) have chosen to call it crystalline vitamin B₁₂. Working at the Research Laboratories of Merck and Co., Inc., at Rahway, N. J. since 1942, this group of investigators has devoted its attention to the isolation of the anti-pernicious-anemia factor in liver, and has finally obtained a crystalline product which, in microgram quantities, has produced positive hematological responses in patients with Addisonian pernicious anemia. The compound isolated crystallizes in the form of small red needles which do not liquefy below 300°. In one patient a hematological response was obtained in a patient

* Leitner, Z. A.: Etiology, diagnosis and treatment of early vitamin-deficiency states. *B. M. J.*, May 15, 1948, 917-922.



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At about the same time, Smith (5) in England, working in the Research Division of Glaxo Laboratories, Ltd., reported the isolation of two red amorphous pigments from ox liver, both of which were highly active in pernicious anemia. Smith had already seen the work of Rickes et al. and thought that the vitamin B₁₂ of the American workers appeared to be the pure anti-pernicious anemia factor. While Rickes did not mention any effects of the crystalline product on the subacute combined degeneration of the spinal cord, Smith found both of his fractions effective for the neurological lesions.

This pure substance from liver, named vitamin B₁₂, possessing such high specific potency, becomes a focal point in the field of nutrition today.

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Indian Salt

In India, common salt is obtained chiefly from the evaporation of sea-water or salt-spring water. Four ounces of salt may be obtained from one gallon of sea-water. Evaporation is carried out in pans. This type of salt, referred to as "Indian salt" contains about 88 per cent sodium chloride. However, some of the salt used in India is mined as rock salt which yields about 98 per cent of sodium chloride. The "Indian salt" contains, in addition to sodium chloride, the sulfates of calcium, magnesium and sodium and magnesium chloride. Many natives prefer the "Indian salt" to purified table salt inasmuch as it tastes "saltier" and less is required.

Mhaskar, K. S.: Nutritive value of common salt. *J. Indian Med. Assn.*, Jan. 1948, V. 17, No. 4, 120-127.

Protein from the Indian Ground Nut

In India, where today starvation conditions are prevalent, it is the opinion of K. V. Giri (1) that the urgent need of the poorer sections of the population is protein and vitamin B₁. One of the great difficulties is in finding protein food of high biological value, since meat, eggs and milk are at present extremely scarce. In fact there is no prospect of any improvement in the near future. There would have to be a general development of livestock breeding, the raising of fodder crops and a great increase in the fish industry. Meat eating is interdicted on religious grounds among many sects in India. Hope seems to lie in the utilization of vegetable proteins. Predigested protein obtained from the ground nut cake (after expression of the oil) contains 61 per cent total nitrogenous extractives, 14 per cent amino-acids and peptones, and about 300 I. U. per 100 gms. of vitamin B₁, being thus superior to marmite and other yeast extracts. A suitable mixture of ground nut, cotton seed and sesame flour, predigested and concentrated, promises to furnish an answer to the prevailing lack of protein and thiamin.

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Abstracts on Nutrition

WILKINSON, J. F.: *Folic acid*. (Brit. Med. J., April 24, 1948, 771-776).

There are several "folic acids" and perhaps some confusion still exists with respect to the interrelationships of vitamin B₁₂, L. casei factor, etc., but the author in his clinical experiments used synthetic pteroyl glutamic acid. Briefly, he was able to obtain good hematological responses in Addisonian anemia, but folic acid did not prevent the onset of peripheral nerve degeneration or cord changes even in cases under conditions of excellent blood remissions, nor did folic acid have any improving influences on already established neural involvement. Furthermore, many persons in good folic acid remissions still showed a dis-

turbed smear picture characterized by persistence of macrocytes. The author does not consider folic acid the best or cheapest form of treatment for pernicious anemia and it must *not be given alone* to patients with neurological symptoms. He describes achrestic anemia as similar to pernicious anemia but with normal gastric juice and no neurological manifestations: usually there is a comparative failure of response to treatment by anti-pernicious anemia agents.

KARAMCHANDI, P. V.: *Sprue syndrome in India*. (J. Indian Med. Assn., March 1948, V. XVII, No. 6, 196-198).

The author, as medical consultant in the Indian Medical Service during the war, noted that vitamin

B deficiency played an important part in the development of a syndrome manifesting itself in varying degrees of emaciation accompanied by diarrhea, indigestion, glossitis and anemia. Some of the names applied to this syndrome are: para sprue, incomplete sprue, chronic jejunoileal insufficiency and vitamin B deficiency syndrome allied to sprue. The outward symptoms of sprue depend upon what portion of the digestive tract is chiefly affected. A duodeno-jejunal site causes diarrhea containing excess of split fat or total fat or both. An ileal site will not affect the normal fat content of the stools. A colonic site may cause mucus and blood to appear in the stools. A gastric site leads to gastritis and anemia. The pathological lesion is essentially an injury to the columnar epithelium with superimposed infections.

The author ingeniously divides his cases as follows: (1) Diarrhea and dyspepsia, (88 cases), (2) Diarrhea, dyspepsia and glossitis (96 cases), (3) Diarrhea, dyspepsia, glossitis and anemia (54 cases) and (4) Diarrhea, dyspepsia, glossitis, anemia and fatty stools (four cases). Gastric acidity was 100 per cent normal in group one; there was 15 per cent achlorhydria in group two and 20.9 per cent in group three. Macrocytic anemia was present 10.2 per cent of the first group, 15.6 per cent of the second group, 26 per cent of the third group and 100 per cent of the fourth group. Dietary treatment consisted of frequent feeding of milk, kher, rice, fruit, vegetables, cereals, vegetable, eggs, toast, chicken, etc., and vitamins administered as raw liver juice flavored with lime juice, lemon water and orange juice containing dilute HCl. Advanced cases received nicotinic acid and ascorbic acid tablets, and liver extract parenterally. At the time this work was done folic acid obviously was not available. The author states: "The ancient custom of cow conservation, whose milk wards off disease, is based on sound lines," and milk constitutes a prophylactic measure. Folic acid is recommended, along with thymic, in selected cases.

LITMAN, N. N. AND BOSMA, J. F.: *A preliminary report in the association of growth failure and poliomyelitis.* (Journal-Lancet, May 1948, V. 68, No. 5, 185-187).

Using the Wetzel "Grid for Evaluating Physical Fitness" on examination of 856 children of whom 133 were patients with polio in 1946, it was found that unsatisfactory growth preceded the attack of polio in 66 per cent of the patients, as compared with its simultaneous appearance among only 20 per cent of the controls. Such a difference is certainly statistically significant. There was a comparative scarcity of patients in the pre-pubertal stage of development.

MEDOVY, H.: *Well-water methemoglobinemia in infants.* (Journal-Lancet, May 1948, V. 68, No. 5, 194-195).

The author says that 12 cases of the title affliction have been detected in rural Manitoba and Ontario. The infant, usually under two months of age, is brought to the physician because of cyanosis. This is

due to abnormal amounts of methemoglobin in the blood, caused by the use of well-water containing high degrees of contamination with nitrates. The substitution of pure water causes the cyanosis to disappear within 36 hours. Some of these cases are suspected of having congenital heart disease. Wells producing water with such marked nitrate contamination usually are situated in barn-yards, and the disease is therefore a rural one.

STANUS, H. S.: *Disorders of the nervous system due to malnutrition.* (Brit. Med. J., Feb. 21, 1948, 342-343).

A close study of the neurological manifestations occurring persons suffering from malnutrition shows the disorders are of a sensory nature, indicating a wide (often reversible) effect on the cortex, both cerebral and cerebellar and on the subcortical nuclei. The dietary deficiency relates, in such cases, to proteins and B-group vitamins. It is the author's belief that riboflavin deficiency is responsible for the physiological changes in these cases, by producing a hypoxia through interference with carbohydrate metabolism, in which process the vitamin in question plays a vital enzymatic role. The failure of glucose metabolism occurs in the neuropiles of those areas of the central nervous system which have a high metabolic rate.

BARWIN, H., REARNON, H. S., WINN, J. S., TENBRINK, M. S., STERN, M. L. AND ENGEL, M. G.: *Relation of lesions of the tongue in children to niacin deficiency.* (Am. J. Dis. Child., Dec. 1947, V. 74, No. 6, 657-668).

Lesions of the tongue are common in children. Four types of lesions of the tongue were observed in the present series: acute glossitis; glossitis migrans (geographic tongue); mild swelling of the tongue; and fissures of the tongue. Large doses of nicotinamide (U. S. P.), eight to 20 mg. per kilogram of body weight were used on a group of children and results compared with an untreated group. The acute glossitides improve spontaneously or after chemotherapy. Swollen and fissured tongues showed a larger proportion of improvement on treatment than without treatment. No complete cures were obtained. Geographic tongue was not influenced by nicotinamide. Diet played no apparent role in the etiology. Niacin has a favorable effect on the nutrition of the tongue, but there is no reason to believe that common tongue lesions in children are due to niacin deficiency.

HARRIS, R. S.: *Food composition and nutrition programs.* (Nutrition Reviews, Feb. 1948 V. 6, No. 2.).

In a study of the nutritional value of foods eaten by the Otomi Indians in the Mezquital Valley of Mexico, it was found that chemical analysis of their common foods revealed a food intake superior to that of an urban group in the United States which was studied at the same time. This explains why pronounced clinical nutritional deficiency among these Indians was not common, in spite of the fact that

Liver Integrity and the Protein Intake

That the prognostic outlook in fatty infiltration of the liver and in portal cirrhosis is no longer poor is a reflection of the significant advances made in the treatment of these conditions. Modern-day therapy is based on the recognition of the role played by lipotropic agents, such as choline, when given in conjunction with a diet high in biologically complete protein and low in fat.

While formerly carbohydrate was considered the chief factor in the maintenance of hepatic function, protein is now regarded one of the most important dietary principles in safeguarding the integrity of the liver. Unless given with adequate amounts of protein, carbohydrate alone is ineffective. For this reason, the modern dietary of many hepatic affections provides protein in abundance in addition to carbohydrate.

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consumption of meat, dairy products, fruits and vegetables was extremely low. They live on tortillas, pulque (fermented juice of the century plant) and numerous edible plants growing in their area, such as malva, hediondilla, tuna, nopales, maguey, garambullo, yucca, purslane, pigweed, sorrel, wild mustard flowers, lengua de vaca, sow-thistle and cactus fruits. There are many parts of the world where the American pattern of good nutrition ought not to be advocated because the foodstuffs which assure good nutrition for us are

not often those which can most effectively and economically nourish the people of other countries. Some of the foodstuffs grown in the United States are less nutritious than the same strains grown in Middle America (e. g. Honduras). These southern food articles are flown North in a frozen state to the Massachusetts Institute of Technology where a five year program of analysis will greatly help to place on a sound basis the solution of nutritional problems in these areas.

Editorial.

ASCORBIC ACID IN THE TREATMENT OF HEMORRHAGE IN PEPTIC ULCER

WHILE THE MAJORITY OF PATIENTS with serious hemorrhage from peptic ulcer pass through the ordeal and recover, irrespective of the type of medical treatment employed, a sufficient percentage die from hemorrhage to put us on guard and rob us of that sense of security which most clinicians formerly felt. Arguments still continue as to whether to starve or feed the bleeding ulcer patient, but the majority of American physicians believe in withholding food and give only cracked ice, while the patient is rendered quiet with an ice cap on the epigastrium.

Blood transfusions may be employed if thought advisable or imperative. While surgical intervention is usually undesirable because of technical difficulties in locating the bleeding vessel and because of the patient's poor condition as a surgical risk, it must nevertheless be undertaken if all other measures give promise of failing.

When presented with the emergency of a patient bleeding uncontrollably in spite of repeated blood transfusions, the possible role of a deficiency in ascorbic acid ought to be considered. The writer has recently seen two such cases in which the intravenous administration of 100 mgm. of ascorbic acid every two hours has caused a cessation of hemorrhage and led to recovery. Both cases prior to the use of ascorbic acid were moribund. It is assumed that a vitamin C deficiency had resulted from the use of a restricted diet over long periods of time.

As a corollary, it should be again emphasized, as it has been often emphasized by many authors, that the diet of the ulcer patient ought to be fortified with ascorbic acid, if for no other reason than the favorable influence of this vitamin in ease of hemorrhage.

Book Review

THE DIGESTIVE TRACT IN ROENTGENOLOGY,
by Jacob Buckstein, M.D. 889 pages, 1030
illustrations in 659 figures. (\$16.00) J. B.
Lippincott, Philadelphia, 1948.

Out of his tremendous experience, Buckstein wrote his new book. It deals with the roentgenological examination of the digestive tract. The routine methods of examination are taught. The normal and pathological conditions of the digestive tract are discussed extensively. Besides the routine methods, Buckstein adds some studies with the thin layer technique for the examination of the mucosal surface of the gastrointestinal tract. The author's tremendous material contains illustrations of practically any pathological condition of

the digestive tract. The clear, precise writing makes this book valuable to students as well as to specialists, and it will be a welcome addition to their library. The book contains many case reports with clinical findings, roentgenological observations, and autoptical controls. There are more than 1,000 illustrations, representing roentgenograms and photographs of surgical and autopsy specimens. The bibliography, added to every chapter, is not entirely complete.

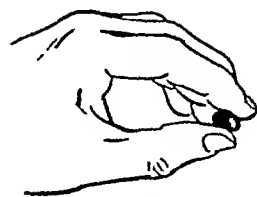
The text is clear, the print and reproductions are excellent and speak well for the publisher. We welcome this publication which certainly will become a standard reference book for all those interested in the gastrointestinal tract.

FRANZ J. LUST



Mr. Preen always SHAVES his breakfast

When will people like Preen discover that a thousand missed breakfasts can add up to one subclinical vitamin deficiency? You know that chronic breakfast-skipping eventually can evoke a half-sick, half-well complaint just as easily as chronic hurrying, chronic worrying or faddist dieting. Since these cases are usually the result of months—perhaps years—of nutritional sidestepping, they often need immediate vitamin supplementation in conjunction with dietary reform. To offset the whims of the patient's appetite and the wide variances in food values, many physicians continue vitamin supplementation for the duration of treatment. Very often their choice is DAYAMIN, Abbott's potent multivitamin capsules. Each easy-to-take capsule contains six essential vitamins as well as pyridoxine and pantothenic acid. One capsule daily as a supplement, more as a therapeutic agent. Your pharmacy has DAYAMIN in bottles of 30, 100 and 250 capsules. If your patients don't like capsules, prescribe golden DAYAMIN LIQUID with the citrus-like taste—in bottles of 90 cc., 8 fluidounces and 1 pint. ABBOTT LABORATORIES, NORTH CHICAGO, ILLINOIS.



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General Abstracts Of Current Literature

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CLINICAL MEDICINE

STOMACH

BERRY, L. H.: *Atrophic gastritis and malnutrition*. (Proceed. Central Soc. Clin. Res. V. 20, p. 59, Nov. 1947).

In patients with chronic atrophic gastritis there is a definite relationship to malnutrition which establishes the disease as being of primary rather than inflammatory origin. Malnutrition not due to disease was shown to follow an economic pattern. The trend shown was based on studies on 706 dyspeptics gastroscopied 1,000 times preceding World War II and 297 dyspeptics gastroscopied 364 times during the war years. Chronic "atrophic gastritis" was three times higher in the pre-war group. Unemployment for periods of two to eight years before study was common in the pre-war group of patients. Improvement of the economic status during the war resulted in better nutrition and could be correlated with a decrease in the occurrence of chronic "atrophic gastritis."

TODD, R. McL.: *A review of 112 cases of congenital hypertrophic pyloric stenosis*. (Arch. Dis. Child., V. 22, p. 75, June 1947).

A common disease encountered in the infant during the first few weeks of life is congenital hypertrophic pyloric stenosis. The author reviews 112 cases treated in the wards and out patient department of the Leicester Royal Infirmary. A series of 40 consecutive cases were followed clinically and radiologically. Physical and mental development were not found to be impaired. The delay in gastric emptying time was in proportion to the severity of the condition. Medical routine treatment is recommended unless the patient is grossly dehydrated. If a seven-day medical trial is ineffective the question of surgery should be considered. Surgery is advocated if the dehydration is severe. No surgical intervention should be planned if there is an infection which would subject the patient to the risk of fatal gastro-enteritis.

BOWEL

FRAWLEY, THOMAS F. AND GOADE, WILLIAM J.: *Benign ulcer of the fourth portion of the duodenum*. (Am. J. Roentg. and Radium Th. 57, 3, 333. March 1947).

The authors describe the rare case of a benign ulcer of the duodenum in its fourth portion. The patient had a long history of epigastric pains and distress. About six years previous to the examination she had an episode of hematemesis with syncope.

Lately vomiting one hour after meals had occurred. There was no loss of weight. At the roentgenological examination a pea-sized ulcer crater was found in the fourth part of the duodenum with associated spastic narrowing which could be seen to relax during fluoroscopy. The duodenum was dilated proximally. Mucosal markings could be seen converging toward the area of ulceration. There was a slight four hour residue in the stomach.

The gastric analysis revealed high values for free and total hydrochloric acid.

FRANZ J. LUST

BLACK, B. M. AND McEACHERN, C. G.: *Redundant blind segments of intestine following side-to-side anastomosis with division of the bowel*. (Surg. Gynecol. and Obstet. V. 86, p. 177, Jan. 1948).

The blind loop of intestine proximal to the point of side-to-side anastomosis may become the site of serious complications. If this loop is too long it may dilate into a pouch three to four times its normal diameter. Peristalsis carrying contents into the blind pouch may result in filling with feces, ulceration, or perforation. The symptoms are variable and may be altogether absent. The danger of a blind dilated bowel segment is the potential source of obstruction. In five cases operated on by the authors for exploratory purposes excessive lengths of blind proximal intestine segments were found. The symptoms were those suggesting obstruction. The authors do not believe that redundancy per se is an indication for reoperation and removal of the blind loop; they believe that surgery for its correction should be entertained only when symptoms are attributable to the redundant loop.

CONNOLLY, E. A. AND LEMPKE, A. W.: *Jejunal malignancy*. (Surgery, V. 21, p. 901, 1947).

Malignancy of the jejunum is rare. Among the suggested explanations are absence of sharp angulations, the presence of alkaline contents, the fluid condition of the contents, the absence of stasis and the relative mobility of the region. Diagnosis is not readily established from the nature of the symptoms. Nausea, dizziness, weight loss, anemia, weakness and occasional periods of obstruction are the commonest symptoms. Changes in bowel habits may not be present. Pain is more or less in proportion to the degree of obstruction: epigastric pain usually occurs only

when metastasis is present. Roentgenologic examination may show constriction, delayed emptying or a filling defect of the small intestine, but negative findings are very common. Exploratory operation should be considered if the evidence suggests a possibility of malignancy. Resection with anastomosis is recommended. Prognosis is poor and mortality is high. Recurrence would be prevented by early surgery and wide resection. The authors report two cases successfully operated and surviving more than five years.

DOUB, HOWARD P. *Malignant tumors of the small intestine.* (Radiology 49, 4, 441. October 1947).

The recognition of malignant tumors of the small intestine depends upon a careful evaluation of the clinical features, including laboratory studies, and, most important of all, a careful roentgen study. Much of the improvement of the recognition of these tumors has resulted from the more widespread use of serial study of the small bowel during the past decade. The highest percentage of malignant neoplasms of the small bowel are adeno-carcinomas. Lymphosarcomas are second in numerical order and carcinoid tumors a poor third. Grossly the tumors are of two types: constricting and fungating or polypoid. The constricting type produces mechanical obstruction by narrowing the intestinal lumen, while with the poly-

poid type obstruction is due to the bulk of the tumor or to intussusception.

The clinical picture is usually one of a progressive loss of weight and strength and varying degrees of anemia. Pain is a prominent symptom. A change of bowel habit is usually present and this may go on to an acute obstruction which brings the patient to seek relief. A palpable tumor is an important and significant finding. Distention is often present. Unusual peristalsis is common.

The roentgen picture is one which is common to the neoplasms of the gastrointestinal tract. The abnormal findings may consist of an area of narrowing of the lumen of the bowel and dilatation proximal to it. Marginal or central filling defects may also be present, with obliteration of the mucosal markings in the involved area. Doub's series of 52 malignant tumors of the small intestine includes twenty-one carcinomas of the duodenum and one lymphosarcoma. In the peri-ampullary type, jaundice, often of an intermittent character, is a prominent feature. Pain is the outstanding symptom. In about 50% of the cases a palpable tumor is present. Secondary duodenal displacement, peristaltic reversal, and gastric retention is found. The series includes 14 primary malignant tumors of the jejunum. Lymphosarcoma occurred eight times, mostly in the ileum. Carcinoid or argentaffine tumors were found in four instances.

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GOLDEN, ROSS.: *Some problems in abnormal intestinal physiology associated with peritoneal adhesions and ileus.* (Pancoast lecture). (Am. J. Roentgen. and Rad. Ther. 56, 5, 555. November 1946).

The author discusses the significance of certain observations on the small intestine in cases of peritoneal adhesions, obstruction and ileus. Possible explanations for some of these phenomena are given.

Ileus is more than mere dilatation of the intestine. As ordinarily used, this term includes far-reaching disorders, both within and outside of the intestinal wall. The intestine is highly vulnerable to acute distention, but shows a remarkable ability to compensate for gradually developing obstruction with slow dilatation. Hypoproteinemia and edema are frequent complications of mechanical ileus and may be responsible for a superimposed paralytic ileus.

The trouble caused by peritoneal adhesions appears to be more than the effect of mere mechanical pressure or angulation. A localized disturbance in the motor physiology of the intestine may occur at the site of an adhesion. This is manifested by narrowing of the lumen which may persist after death. The mechanism by which this is produced is not clear. Exact knowledge concerning the histologic changes within the wall at the site of adhesions is not available. It seems possible that a mechanical stimulus from the pull of the peristaltic contraction transmitted caudad through the adhesions to the wall ahead of the peristaltic wave may play a part in causing the localized narrowing.

FRANZ J. LUST.

SANDERS, L. C.: *The early diagnosis of carcinoma of the colon and rectum.* (Rev. Gastroent., March 1948, V. 15, No. 3, 193-207).

In cancer of the ascending colon, anemia, often resembling pernicious anemia, is a distinctive and early feature. In cancer of the descending colon, obstruction is frequently the first sign. In cancer of the rectum, constipation, rectal fullness and bloody stools give the clue.

MONAT, H. A.: *Constipation.* (Rev. Gastroent., March 1948, V. 15, No. 3, 242-244).

Chiefly notable because author describes a variety of constipation occurring in psychoneurotic cases who find a pathological pleasure in not moving their bowels for seven to nine days, and such patients can be benefited only by appropriate psychotherapy.

DAWSON, R. L. G., AND HARDY, R. H.: *Diverticulitis presenting as emphysematous cellulitis of leg.* (Brit. Med. Journ., Mar. 13, 1948, 498-499).

Two very similar cases are described in each of which a diverticulitis of the descending colon ruptured and formed a fistulous tract over the inguinal

ligament with a resulting fatal cellulitis of the left groin and thigh. One point of interest was the obvious difficulty of figuring out the origin of the severe superficial lesion. Another point of interest was that in neither case was *B. Welchii* found on culture. In one, only *B. coli* was cultured and in the other both *B. coli* and *S. faecalis*. One case developed the condition while in the hospital for the removal of a neuroma from her back, but the other came in with the thigh lesion and died promptly. X-ray detected the diverticulum in the former case and post-mortem examination proved its presence in both.

LIVER AND GALLBLADDER

VADHEIM, J. L. AND NELSON, E. P.: *Congenital atresia of bile ducts.* (Northwest Med., March 1948, V. 47, No. 3, 197-199).

Several hundred cases of congenital atresia of the bile ducts have been reported. In some cases so diagnosed the presence of inspissated bile was the cause of the jaundice. The persistence of high grade jaundice for a month following birth should arouse suspicion of atresia. It is remarkable how long an infant may live even when the condition is not corrected, some living to fifteen months, although the average duration of life is seven months. The average icterus index was 125 in one series of 45 cases (Ladd). Clay-colored stools are present and the urine is positive for bile pigments but negative for urobilinogen. The Van den Bergh reaction is prompt and direct. Moderate anemia, enlargement of liver and spleen and ascites are frequent symptoms. Operation is not always successful but anastomosis of the gall bladder to the stomach, provided the cystic duct is patent, is the easiest surgical solution, as a rule.

ZUCKERBROD, M., LITWINS, J., ROGLIANO, F. T. AND JELLINGER, D.: *Amebic liver abscess.* (Ann. Int. Med., April 1948, V. 28, No. 4, 798-815).

Three cases of amebic liver abscess occurring in a Station Hospital in New York in a relatively short period of time illustrate the fact that, particularly in returned service men, the condition should be more often suspected and furthermore the condition is not a rare one. In only one of the three cases were amebae found in the stools. About nine per cent of cases of amebiasis with clinical symptoms develop liver abscess. Usually the right lobe near the dome of the diaphragm is involved. Rupture into the pleura or lung is the commonest complication. X-ray studies are of value in locating the abscess and determining its size. Emetine hydrochloride subcutaneously (65 mg. daily for a period of eight to ten days) is the really specific treatment. A second course may be given after a month if necessary. Because of the presence of intestinal amebiasis associated, diodoquin (0.6 mg. thrice daily for ten days) is preferred because of its lack of hepatotoxic effects.

Pancreas Function Tests

By

H. L. POPPER, M.D.

and

H. NECHELES, M.D.

CHICAGO, ILLINOIS

DISEASES OF THE PANCREAS have been receiving more publicity lately. But they still are not getting the attention they merit. This is due in part to their relatively rare occurrence and in part to their lack of characteristic clinical features. The pancreas is in a location where it can hardly be palpated and where even marked changes in its size, shape or consistency often escape detection even by X-ray and its secretory function has such a large reserve capacity that only very extensive pathologic processes cause a visible deficiency of its digestive action. Consequently, diseases of the pancreas seldom offer conclusive clinical features, especially not in the early stages.

Clinicians and research men have striven for years to find a specific test which would indicate the presence of pathology of the pancreas. In the following, a short review is presented of the various methods which were in use, or still are in use, and of their respective values.

Visual inspection of the pancreas or of its functional activity by some kind of endoscopy is not possible and no way has yet been found to make the pancreas visible by X-ray. Occasionally, pathology in the pancreas will cause certain changes in the X-ray appearance of stomach or duodenum. However, this is usually limited to cases with marked pathologic changes of the pancreas, and it is not a constant finding.

No substance has yet been found which is excreted only in the pancreatic juice and which, similar to the excretory tests of kidney and liver would make possible the simple chemical evaluation of the pancreatic condition. The only methods which are available for obtaining such information are based upon the study of the disturbances of pancreatic secretion, primarily the external secretion and at times the internal secretion. Both of these are being studied under normal conditions, as well as under experimentally induced hyperactivity of the gland.

The external secretory function of the pancreas consists of manufacturing pancreatic juice and of

delivering it into the duodenum. The main importance of the pancreatic juice lies in its alkalinity and its digestive enzymes. As mentioned before, the external pancreatic secretion has a very large reserve capacity so that even a small portion of normal pancreatic tissue is sufficient to provide enough pancreatic enzymes to maintain a more or less normal digestion of food. Pathologic processes which involve only part of the pancreas or cause only a partial obstruction will usually not lead to noticeable changes in the digestion of food. Consequently, only a lesion that interferes with the glandular activity of almost the entire gland can be expected to lead to digestive disturbances. The same disturbances can be expected when the lesion is not in the glandular tissue, but in or at the main pancreatic duct where it blocks the pancreatic juice and prevents it from reaching the intestinal tract. However, such is the case only if there is but one pancreatic duct. If an accessory duct is present, it will discharge its share of juice into the duodenum and no digestive disturbance may manifest itself. Only 20% of autopsies had just one duct. We can expect lack of pancreatic enzymes in the intestinal tract in these cases only if both ducts are obstructed.

The finding of a lack of pancreatic enzymes in the intestinal tract, and the subsequent disturbance in digestion, permits two conclusions: the presence of a very extensive lesion of the pancreas, comprising most of the gland, or a complete obstruction of the pancreatic ducts.

Until recently, clinicians were satisfied with tests that would show whether there was any pancreatic secretion at all. Lack of pancreatic secretion, as e. g., in pancreatic achylia, played a much more important role in their diagnoses than it does nowadays, because now we know that it is quite rare. They had several methods to ascertain the presence or absence of pancreatic juice in the gastro-intestinal tract.

Volhard's test was based on the observation that a reflux of bile and pancreatic juice into the stomach occurs after introduction of large amounts of fat into the stomach. In the test, 200 cc. of oil were introduced into the stomach through a tube. The gastric contents were evacuated after half an hour and were tested for trypsin. Presence of trypsin was an indication of the presence of pancreatic juice, but it could not be used for a quantitative evaluation.

Examination of the stools for trypsin after a test

From the Department of Gastro-Intestinal Research, Medical Research Institute of Michael Reese Hospital, Chicago, Ill.

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meal and a laxative had been given. The laxative, by speeding up intestinal motility, prevented destruction of the pancreatic trypsin in the lower part of the gastro-intestinal tract.

Schmidt's nucleus test. Nuclei of cells or, more correctly, nucleic acids, are digested by a pancreatic enzyme, nuclease. Therefore, lack of digestion of ingested nuclei was considered to be indicative of lack of pancreatic secretion. A certain kind of dyed vegetable nuclei were given with the food. Then the feces were examined for presence of the nuclei which were not supposed to be found under normal conditions.

Sahli's glutoid capsule test. Capsules of formol treated gelatin were filled with a substance which, after absorption, is excreted through the kidneys and which can be detected easily in the urine, as e. g. methylene-blue or potassium iodide. These capsules were supposed to be digested by pancreatic juice only, and the presence in the urine of the substance which was contained in the capsule proved the presence of pancreatic juice in the intestinal tract.

Somewhat similar was Winternitz's Sajodin test. Sajodin, an organic iodine compound, was thought to be split only by the action of pancreatic enzymes. The presence of iodine in the urine, after ingestion of Sajodin, was considered evidence of the presence of pancreatic juice in the gastro-intestinal tract.

Another older test, which was thought to be indicative of diseases of the pancreas in general, not only of complete lack of external pancreatic secretion, was the Cammidge reaction. By a complicated chemical analysis of the urine a substance was isolated which was presumed to be diagnostic for lesions of the pancreas because it was found only in patients with pancreatic disease. The publication of this test was received with much enthusiasm and was followed by some very favorable reports, but continued critical observation contradicted the claims of its originator.

Another test which caused widespread interest in previous years was Loewi's adrenalin test. Instillation of adrenalin into the eye was said to cause dilatation of the pupil in case of disease of the pancreas. Of course, this test is by no means specific for pancreatic disease.

All these methods are now obsolete and almost forgotten, not because we have a better test to replace them, but because most of them were only meant as indicators of a complete loss of pancreatic function and because all of them were unreliable and often misleading.

The present methods which are in use or which might be used for studying pancreatic function are:

Examination of the stools for undigested food. This is the only one of the older methods, which has withstood the test of time. Pancreatic juice is the main source of fat and protein splitting enzymes in the intestinal tract. Hence the presence of increased amounts of undigested fat and of undigested muscle

fibers indicate deficiency of pancreatic function, provided that other causes for creatorrhea and steatorrhea have been excluded. Regarding the problem of fatty stools, I refer to a recently published informative paper by Kirschen and Weinberg.

For this test, the patient must be put on a diet with standard contents of fat, carbohydrate and protein. Quantitative chemical analysis of the fat and nitrogen in the feces indicates the degree of digestion of the diet. However, as stated before, only extensive disturbances in the external pancreatic secretion will show significant changes in the feces. In the latter case, we have to rule out first of all, deficient absorption due to hyperperistalsis of the bowels, since shortened exposure of the intestinal contents to the action of the digestive juice causes elimination of undigested food.

Duodenal intubation and aspiration of duodenal juice. The qualitative and quantitative determination of amylase, lipase and trypsin in the aspirated juice gives crude information on the secretory state of the pancreas. However, duodenal intubation requires co-operation on the part of the patient and it can hardly be done in very sick patients. Moreover, duodenal intubation requires practice, otherwise the number of failures may be quite high. If no enzymes are found in the aspirated juice, rarely can one tell whether or not pancreatic secretion is really absent unless the presence of the tube in the duodenum was checked by fluoroscopy. Besides, the admixture of gastric juice and of bile makes a quantitative determination of enzymes impossible.

Wohlgemuth reported in 1908 that an increase of amylase could be found in the blood in acute disorders of the pancreas. Further studies have shown that not only an increase of amylase, but also of lipase is demonstrable in the blood serum. The blood amylase test, to date still is the most valuable indicator for acute pancreatic diseases.

Blood amylase and blood lipase determinations are reliable information only if performed during the first few days of acute disease of the pancreas or following an acute flare-up of the process. They are of little help in subacute or chronic forms of pancreatitis and in the other pathologic conditions of the pancreas, such as in atrophy or sclerosis, in carcinoma or cyst formation though we may occasionally find an increase of serum lipase in a case of carcinoma of the pancreas. Serum amylase and lipase may be increased in such diseases as mumps and typhoid fever. Rarely there is a doubt about a differential diagnosis between these diseases and disease of the pancreas.

These two enzymes are excreted mainly by the kidneys and are found in the urine even for somewhat longer periods of time than in the blood. However, the excretion in the urine is dependent upon kidney function. This fact and the variations in enzyme values due to fluctuations in urinary pH and

concentration make the blood test much more dependable.

The close local relation between the secretory glandular tissue of the pancreas and the insulin-producing islets of Langerhans accounts for the fact that pathologic changes of the glandular tissue often are associated with disturbances in the carbohydrate metabolism. Indeed, the study of the carbohydrate metabolism provides us with a simple method of demonstrating certain lesions of the pancreas. However, similar to the glandular tissue of the pancreas, the insular tissue has a large reserve capacity, and a fraction of the islets is usually sufficient to regulate the carbohydrate metabolism. Therefore, only lesions which involve a large portion of the pancreas can be expected to cause diminution of insulin secretion. The disturbance in the carbohydrate metabolism is to some degree in proportion to the severity of the pathologic process and in lesions where the pancreatic tissue is severely damaged we will generally find increased fasting blood sugar. Cases with diffuse pancreatic lesions where the pancreatic tissue is only slightly damaged frequently have a normal fasting blood sugar. In such cases a disturbance in the carbohydrate metabolism can often be demonstrated by a glucose tolerance test. In these cases the insulin production is sufficient to control carbohydrate metabolism in the fasting state, but it is inadequate to dispose of additional sugar in the normal way. An abnormal glucose tolerance curve is, however, a frequent finding and it is often due to extra-pancreatic causes. Therefore, its presence can be used as a diagnostic aid only in a limited sense.

The double glucose tolerance tests may be more useful. Staub, as well as Traugott, has shown many years ago, that disturbances of the insulin production by the pancreas reveal characteristic changes in the second part of the double glucose tolerance test. Following the second dose of glucose a larger rise of the blood sugar may occur than that following the first dose or two hours after the second dose the blood sugar may fail to drop to or below the control level. In our experience, this test proved to be helpful, especially in subacute forms of pancreatitis. It may be of value also in cases of sclerosis of the pancreas and in some cases of pancreatic carcinoma. It should be noted, however, that no glucose tolerance test should be performed in acute pancreatitis. The hyperglycemia following glucose administration stimulates the external pancreatic secretion and is one thing we should definitely avoid, because it may aggravate the acute process in the pancreas.

These tests, with the exception of the glucose tolerance curve, are based on the assumption that any degree of pathology of the pancreas will show a noticeable deviation from normal pancreatic function. However, this is so only rarely, and as it is mostly found in extensive or acute processes, the diagnostic value of these procedures is limited.

A step forward was the attempt to stimulate the

pancreatic secretion by oral or duodenal administration of certain substances during the duodenal intubation. It was hoped that this might reveal secretory dysfunctions that otherwise would have escaped notice.

In 1922 Katsch injected ether through the duodenal tube. Under normal circumstances this was followed by a large increase in pancreatic secretion. The lack of such a response indicated pancreatic insufficiency. Another investigator introduced hydrochloric acid into the duodenum. Still another method consisted of administration of olive oil. McClure used various stimulating foods for the same purpose.

All these methods had the disadvantage that the aspirated material consisted of not only bile, pancreatic juice and stomach juice, which are the normal contents of the duodenum, but also of the introduced substances. Furthermore, ether, though it proved to be an excellent pancreatic stimulant, has the disadvantage that it is an enzyme inhibitor, so that only the increase in volume of pancreatic juice, and not its enzyme concentration could be measured.

French authors, Chiray and his co-workers in 1926, were the first to give their patients secretin intravenously during duodenal intubation. In normal cases they found a marked increase in total volume of pancreatic juice and of pancreatic enzymes, while in 17 out of 29 cases with pancreatic lesions, they found no increase of flow or of enzyme concentration after the stimulation. Voegtlin, Greengard and Ivy in 1934 did not obtain consistent results in similar experiments. Both groups used a secretin preparation containing cholecystokinin and other impurities.

In the meantime, Hammarsten and Agren had succeeded in preparing a more purified secretin free from cholecystokinin and without side effects and Agren and Lagerlöf started clinical experimentation with that preparation. They realized that injection of even the purest preparation of secretin could not be of much value as long as the aspirated duodenal juice was only one portion of a variable mixture of different secretions. Due to the fact that the Swedish secretin did not contain cholecystokinin, it did not cause an increase in bile admixture to the duodenal juice, but the admixture of stomach juice and of swallowed saliva had to be taken care of, if a reliable test was to be developed.

Agren and Lagerlöf solved that problem in all its details in 1936, and they deserve ample credit for that. At that time a method was known for studying the secretory function of the human stomach and of the duodenum by introducing two tubes, one into the stomach and the other one into the duodenum. Agren and Lagerlöf used this principle, and improved it by constructing a double tube. In their experiments they showed that procedures in which only part of the pancreatic secretion is collected are of little value and that only the determination of the total enzyme secretion during a certain period will afford information about the secretory capacity of the pancreas.

They succeeded in collecting practically the entire pancreatic secretion by means of continuous mechanical aspiration with constant negative pressure in the two tubes. Besides, an additional suction tube in the mouth permitted the continuous removal of saliva. Thus they had an experimental set-up where the pancreas was stimulated specifically by a substance void of side effects, and they were able to recover the duodenal contents without admixture of gastric juice or swallowed saliva, and without increased admixture of bile. With this set-up for the first time, a test had been developed which actually made it possible to study the external secretory pancreatic function in cases with normal or diseased pancreas.

Agren and Lagerlöf found that pancreatic dysfunction manifested itself by a decrease in the total amounts of secreted enzymes in some cases of acute pancreatic disease, and of enzymes and bicarbonate in other cases. The secretion test gave positive results in most cases of acute pancreatitis and of chronic pancreatitis, and in some cases of pancreatic tumors, depending upon the location of the tumor. However, a negative test, that means no demonstrable change in the pancreatic secretion, could not be used to rule out the presence of chronic pancreatitis or of a tumor of the pancreas. The secretin test was of particular significance in cases with fatty stools, because a normal pancreatic response to secretin permitted the exclusion of pancreatic dysfunction and offered reliable evidence of an extra-pancreatic cause of the steatorrhea.

In this country, Diamond and Siegel used the secretin test on a large number of patients. They reported that a reduction in enzyme concentration was the earliest evidence of dysfunction of the pancreas and that lesser grades of pancreatic dysfunction could be discovered by this test, which otherwise might have been unrecognized.

Comfort and Osterberg reported similar results with the secretin test. In further studies, they found that the combination of mechoyl and secretin stimulated pancreatic secretion more vigorously than any other drug or combination of drugs which they had tried, and they suggested combined use of mechoyl and secretin as modification of the Agren-Lagerlöf test. Maddock and co-workers used the secretin test successfully in infants and children for the differentiation of pancreatic fibrosis from celiac disease or malnutrition.

Agren and Lagerlöf's secretin test is a real progress. It is the first reliable test of pancreatic function and it is to be expected that, if used more widely and on a larger scale, more and more details will be found that will prove valuable. It is to be hoped also that it will be simplified, because the complexity of the test is an obvious disadvantage for its wide clinical use. It has all the disadvantages of duodenal intubation, plus a few of its own. It takes several hours, requires special chemical facilities and practical experience. The patient has to be cooperative. It cannot be done on a very

sick patient, nor on a patient who vomits or is nauseated.

Extending over a period of almost three years, we have performed hundreds of animal experiments in an endeavor to work out a simple pancreatic function test. Our experiments were based on the observation that vigorous stimulation of the external pancreatic secretion is occasionally followed by an increase in amylase and lipase in the blood. This increase is probably due to the fact that following vigorous stimulation of the pancreas, the duct system of the pancreas is not able to handle the greatly increased amount of secretion. This leads to stagnation of pancreatic juice with back pressure in the duct system, and subsequent absorption of pancreatic enzymes into the general circulation. We thought that this fact might be of diagnostic service in two ways:

1. If a substance by stimulating the normal pancreas, regularly causes increase of pancreatic enzymes in the blood, it is to be expected that the same substance will not cause any increase of blood enzymes in case of diminished secretory ability of the pancreas. Such a procedure would reveal disturbances in pancreatic secretory function such as occurs in chronic pancreatitis, sclerosis or atrophy of the pancreas, or functional insufficiency of the gland.

2. It was reasonable to assume that it should be possible to stimulate the pancreas merely to such an extent that in presence of a normal organ no increase of pancreatic enzymes would occur in the blood, because the duct system would be able to accommodate the limited increase in secretion and would drain it into the duodenum, while in cases with an obstruction to the outflow, an increase of serum enzymes would follow. This procedure might uncover total and partial pancreatic obstruction as found in pancreatic lithiasis, carcinoma of the head of the pancreas, cysts, and in a more functional sense, in subacute pancreatitis.

This was our plan of experimentation. The next step was to find out what drug or combination of drugs could be used to get satisfactory results with a dose that could safely be given to human beings. We used many drugs in various combinations with single and repeated injections in hundreds of experiments on normal dogs and on dogs with ligated pancreatic ducts with atrophy of the pancreas and after various injuries to the pancreas. Finally, in 1943, we were able to conclude our studies successfully and to report a new method for testing pancreatic function which had a real promise for use in the patient. The results were:

1. Intravenous injection of relatively small amounts of secretin does not raise the level of serum amylase or lipase in the presence of a normal pancreas, but does so in the presence of obstruction to the outflow of pancreatic secretion.

2. Stimulation of pancreatic secretion with mechoyl plus secretin, which is the most effective combination

in Comfort and Osterberg's as well as in our experience, causes an increase of pancreatic enzymes in the serum of dogs with normal pancreas, while no increase occurs in cases with sclerosis or atrophy of the gland.

The first procedure, the administration of secretin alone, is a test for obstruction of the pancreas. The second procedure, secretin plus mechoyl, should be used as a test for the secretory ability of the pancreas. Our suggestion for clinical use is to give, first secretin alone, and only if this is not followed by an increase of blood enzymes, to give the combination of mechoyl and secretin. In clinical use, the administration of secretin alone and of secretin plus mechoyl will supplement each other efficiently in the diagnostic results, by revealing obstruction or secretory dysfunction of the pancreas, one of which will be present in almost any case with pancreatic pathology.

We did not have enough pure secretin and we did not have enough clinical cases for clinical evaluation of the test.

Recently, commercial manufacture of purified secretin has been started in this country, and we hope that we will get an opportunity for clinical trial of the test, in the near future. It is a simple test because it consists of only one or two injections and the drawing of a few blood samples for enzyme determination, and I think it will give satisfactory clinical results.

Lagerlöf, who did not know of our earlier work, reported on a similar attempt in the human in a recent publication.

SUMMARY

Due to the hidden location of the pancreas and the paucity of clinical findings, in most cases of pancreatic disease, a pancreatic function test is an essential prerequisite for the improvement of our diagnostic results.

The older tests for pancreatic function were based

on the complete absence of pancreatic juice in the intestinal tract or on vague indirect determinations. These tests, except the stool test, are not in use any longer because they were partly insufficient, partly unreliable, or based on false premises.

The tests which are in use nowadays are:

1. Examination of the stools for excessive elimination of undigested fat, and undigested muscle fibers which, with certain reservations, are suggestive of pancreatic deficiency.

2. Determination of serum amylase and lipase which are reliable indicators of acute pancreatitis.

3. Determination of the fasting blood sugar and of glucose tolerance curves, especially after double glucose administration, which will reveal pathology of the pancreas that involves also the insular tissue of the pancreas. This is of special significance in acute and subacute pancreatitis, possibly in sclerosing pancreatitis and in some forms of carcinoma.

4. Agren and Lagerlöf's secretin test with simultaneous intubation of stomach and duodenum and with aspiration of most of the pancreatic secretion. This is the first procedure which gives us reliable information about the external secretory function of the pancreas. The results of this test are promising and it is to be hoped that it will come into general use.

We have developed a pancreatic function test in animal experiments which, by demonstrating an increase of pancreatic enzymes in the blood after moderate stimulation of the pancreas, indicates obstruction to pancreatic secretion or by revealing the absence of such an increase after vigorous stimulation, shows a secretory deficiency of the pancreatic gland.

Clinical application will have to prove the possible usefulness of this test.

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Critique on Sequelae of Viral Hepatitis *

By

IRVING B. BRICK, M.D.**

WASHINGTON, D. C.

THE IMPORTANCE OF ACUTE VIRAL HEPATITIS during World War II can be demonstrated in terms of the occurrence of 170,000 cases in Army personnel alone (1). It ranked only behind malaria and psychoneurosis, among the medical diseases, causing the greatest number of casualties. The terms viral hepatitis, infectious hepatitis, acute hepatitis, epidemic hepatitis, catarrhal jaundice (in the older literature) or combinations of these terms are used by various writers but all refer to the same disease entity. The epidemiology, symptoms, signs and pathology of the acute attack have been well delineated (2, 3, 4). The experimental transmission of this disease in human volunteers is noteworthy (5). The conception of a disease akin in most respects to the epidemic variety but differing in its mode of transmissibility by parenteral use of blood or blood products, especially plasma, has been clarified and extended. For practical purposes, the pathology and clinical course of this variety of hepatitis — called homologous serum jaundice or hepatitis — do not differ from that of the epidemic or naturally occurring type of hepatitis. Lucké (6) and Lucké and Mallory (7) have presented data on the fatal fulminating variety of hepatitis which occurs in a small but varying percentage of cases in different epidemics.

In this presentation we are primarily concerned in examining the available data to determine whether sequelae occur as a result of an attack of viral hepatitis, the pattern of these sequelae and their recognition. To state the objective another way, we may ask certain questions: Can chronic disability occur as a result of an attack of hepatitis; if so, what is the nature of this disability; how frequently does it occur and when does it occur with relation to the acute attack; how long may it last; finally can cirrhosis of the liver occur as a result of acute hepatitis?

That the answers to these questions are of great importance to the Veterans Administration is indicated by a reported research project which will follow a "pool of 60,000 veterans who picked up jaundice in the service" (8). The excellent Veterans Administration Technical Bulletin (1) on the subject of chronic and residual forms of viral hepatitis was prepared by Dr. Richard B. Capps, who, with the late Marion

Barker, had such a wide experience with the problem in the Middle East during the war. This Bulletin should be "must" reading for anyone interested in the problem. If only a small percentage of the patients who had the acute variety in the services, suffers chronic disability, it will be a sizeable problem in compensation since the number of patients affected by the acute attack was so large.

CHRONIC HEPATITIS SYNDROME

Editorially, attention has been called to the persistence of liver damage after apparent clinical recovery (9). Barker, Capps and Allen (10) in a series of 431 unselected cases of infectious hepatitis found that seventy-six or 18% failed to recover promptly and for prolonged periods exhibited symptoms and signs indicative of persistent hepatic disease, with a tendency toward exacerbations and remissions. The investigators applied the term "chronic hepatitis syndrome" to this group of patients with an acute attack of viral hepatitis in which recovery was not attained within four months. One of the characteristic findings in this group of patients was the increase in abnormal physical findings, symptoms and laboratory data produced by exercise. The authors were careful to point out that the underlying pathological physiology was not well known, nor was the prognosis accurately known. They estimated that this condition of chronic active hepatitis characterized by intermittent periods of disability for months or years develops in from five to 10% of properly managed acute cases and with an incidence as high as 28% under other circumstances.

Caravati (11) noted a somewhat similar sequel to homologous serum hepatitis that followed vaccination against yellow fever with a serum containing preparation. Altschule and Gilligan (12) studied thirty-six persons who had had attacks of catarrhal jaundice one to twenty-nine years previously. Hyperbilirubinemia was found in one out of every four; nine patients had palpable livers and another a palpable spleen. In this group of patients symptoms were absent but the authors concluded that a mild form of chronic hepatitis was frequent in this group.

Kunkel, Labby and Hoagland (13) studied three hundred and fifty patients from the Navy with acute infectious hepatitis. Sixty, or 17%, had an abnormal convalescence which was defined as requiring hospitalization for a period greater than three months. The remaining 83% recovered from the acute attack in less than three months, the average period of illness being fifty-six days. Of the sixty patients with

* From the Department of Medicine, Georgetown University School of Medicine, Washington, D. C.

** Instructor of Medicine, Georgetown University School of Medicine; Associate Visiting Physician, Gallinger Municipal and Georgetown University Hospitals, Washington, D. C.; Consultant in Gastroenterology, Diagnostic Clinic, Medical Center, Georgetown University Hospital.

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abnormal convalescence, forty-seven showed a simple relapse with recovery; two patients, relapse with transition to chronic hepatitis; four with chronic hepatitis with persistent bromsulfalein retention; and seven, persistent hyperbilirubinemia. Significantly, eight patients, or 2.3%, did not recover completely after more than one year of observation.

Klatskin and Rappaport (14) studied two hundred and seventeen cases of presumably cured infectious hepatitis and found that one hundred and eight, or 50% had either symptoms referable to the liver (23%), hepatomegaly (27%) and evidence of impaired liver function (19%) with considerable overlapping of these residuals, one-third of the one hundred and eight patients having two or all of these groups of residuals. The duration and severity of the jaundice during the acute attack seemed to be the only factors in this series which bore any relation to the incidence of residuals.

How does one go about recognizing and diagnosing this syndrome of chronic hepatitis? The history will bring out the time of occurrence of the acute attack, the period of hospitalization, the recurrence of jaundice or other symptoms. The clinical picture is characterized by recurring attacks, lasting one to several months, of severe lassitude and easy fatigability associated with headaches, and discomfort or pain in the right upper quadrant; looseness of stools and intestinal cramps may occur. Fat intolerance is frequently found. Anorexia and weight loss may or may not be present. Mental depression, especially after repeated episodes of these symptoms, may be frequently found, and the similarity to psychoneurosis has been pointed out by several writers. Capps (1) states that the disability is often marked and out of proportion to the general appearance of the patients. Attempts to pursue occupations or do jobs that were easily accomplished before the acute attack lead to extreme degrees of fatigability.

Physical findings are limited to tenderness and enlargement of the liver. Despite the absence of any physical findings, laboratory data may reveal marked impairment of liver function so that the clinical evaluation can not be considered complete unless proper laboratory data have been obtained.

Exacerbations may continue to occur at varying intervals and may be precipitated by attacks of dysentery, malaria, and pneumonia. Exposure to alcohol and anesthetics may also cause exacerbations. Overexertion may be a precipitating factor. The reaction to rest and exercise is thought to be particularly characteristic (1). Physical exertion will increase physical signs and laboratory evidence of hepatic dysfunction while rest may have the opposite effect.

What laboratory tests are most likely to reveal abnormalities in chronic hepatitis? Neefe and Reinhold (15) have studied various liver function tests in infectious hepatitis. In the later stages of the disease, they feel, as does Capps, that the thymol turbidity

and flocculation test was the best single test for the detection of chronic disease. The cephalin cholesterol flocculation, bromsulfalein (five mgm./kilo), quantitative serum bilirubin (one minute and total), and quantitative urine urobilinogen tests comprise the other laboratory tests of value in this situation. All workers feel that the routine usage of a group of tests is necessary, because of the variability of response with individual patients and the different types of mechanisms involved in these tests, all of which are not clearly understood. As incapacitating symptoms may be associated with mild hepatic disturbance that is reflected only by weakly or moderately positive responses with but one or several of a group of tests, it is apparent that the disturbance may be overlooked unless reliable tests are employed systematically and as a group. Of lesser value in this particular problem, while retaining their importance in other types of liver disease, are total and differential protein determinations, hippuric acid test, cholesterol and cholesterol ester determinations, and alkaline phosphatase readings.

In some cases, liver biopsy may afford considerable information. It should be reserved for cases in which the findings, both clinical and laboratory, are equivocal. However, the results of such biopsy may not reveal the complete histological picture, since all parts of the liver may not be involved to the same degree. Furthermore, dysfunction of the liver may not always be mirrored accurately by the histological findings.

We can now attempt to answer some of the questions proposed at the outset of this discussion. There is ample evidence by reliable investigators indicating that chronic disability can occur as a result of an acute attack of viral hepatitis. The nature of the disability is not too clearly understood either physiologically or pathologically. At present, the most one can assume is that the signs and symptoms comprise a "chronic hepatitis syndrome" rather than a proven fixed pathological state. Nonetheless, this is, for patient and physician, a real disease entity with social and economic implications. It may occur as a continuance of the acute attack, complete recovery not intervening. Or it may be a recurrence, soon or late, after apparent complete recovery from the acute attack. Its whole duration is not known but the reports available indicate it lasts longer than a year in some cases. Determination of the eventual outcome is just not known at present.

CIRRHOSIS

Does cirrhosis develop as an aftermath of viral hepatitis or does the chronic hepatitis syndrome go on to cirrhosis? This is the final question to be answered. Lucké (16) studied the structure of the livers from fourteen patients who had recovered from epidemic hepatitis. In all fourteen cases the lobular architecture was preserved and the reticular framework was intact. Slight traces of preceding hepatic damage were observed but in the opinion

of Lucké did not indicate persistent or progressive damage. He feels that a small fraction of the cases of epidemic hepatitis terminate in death within a short period of time. The great majority of patients make a clinical recovery that is complete and apparently permanent. He also feels that since epidemic hepatitis and cirrhosis are common diseases, the occurrence of a previous episode of "catarrhal jaundice" in a cirrhotic does not prove a causal relationship.

Roholm and Iversen (17) and Dible, McMichael and Sherlock (18) studied the same problem by serial biopsies of the liver in patients with acute epidemic hepatitis. They, too, found that most cases of acute hepatitis ended in complete histological recovery but in some cases scars remained. Most interesting are the serial biopsy studies of Krarup and Roholm (19) who presented histological evidence in twelve cases of the development of cirrhosis following an attack of acute hepatitis. In some of these cases the time of development of histologically demonstrated cirrhosis after the acute disease was quite brief. Jones and Minot (20) studied twenty-six cases of catarrhal jaundice in five cases of which portal cirrhosis was diagnosed clinically. In two cases there was necropsy confirmation of cirrhosis and the authors opined that the relationship of hepatitis to cirrhosis had not been fully appreciated.

One wonders whether the sampling of fourteen cases by Lucké is sufficiently significant statistically, in a disease in which all observers concede that 90% of patients do make a complete recovery, to rule out a pathological state between death and recovery. Another factor that may cause confusion is the apparent variability of virulence of the epidemics of acute hepatitis in various locations and groups of patients. This type of variability is highlighted by the recent epidemic of infectious hepatitis with a prolonged course and high mortality rate reported from Denmark. Jersild (21) presented five hundred and fifty cases of infectious hepatitis, three hundred and ninety-six of which recovered in less than three months. One hundred and fifty-four cases were chronic, having a duration of more than three months. In this latter group, mortality up to the time of the report was 67%. The deaths occurred for the most part in women after the menopause. The average duration of the disease in the fatal cases was nine months. At necropsy, the livers were extremely atrophic and corresponded to the picture of subacute yellow atrophy.

Writing at a time when the etiology and pathology of viral hepatitis were not understood, Bloomfield (22) in a paper that has been largely neglected, stated and attempted to answer the problem of the relationship of acute hepatitis to cirrhosis. He recognized the initially acute stage which may go on to death, or more likely, complete recovery. He stated, "It is hard to prove that latent anatomical changes are not present" a fact which remains true to date. The possibility that latent changes may go on to cirrhosis

over a period of years is illustrated by cases of cirrhosis in which a story of acute hepatitis can be elicited many years previously. He developed the thesis that the evolution of cirrhosis from acute hepatitis is analogous to Addis' studies on the course of chronic glomerulonephritis in which, following the initial insult, there may be long latent periods clinically which may be detected by proper studies, and ending, with or without clinical exacerbations, in renal failure.

Recently, Howard and Watson (23) studied a series of one hundred patients, largely from rural communities and non-alcoholic, with cirrhosis. Since previous episodes of infectious hepatitis were found in a significantly greater proportion of patients with cirrhosis than in a similar group without hepatic disease, they believe this lends support to the concept that in certain cases, hepatitis runs a chronic or recurrent course, ultimately leading to the clinical and pathological picture of cirrhosis.

Watson and Hoffbauer (24) presented a group of cases following acute infectious hepatitis characterized by prolonged course, hyperbilirubinemia, hypercholesterolemia, and hyperphosphatemia with the hepatic cells showing little abnormal histology. In these cases the cholangioles were mainly affected, giving rise to a cholangiolitic hepatitis which, in the authors' experience, may go on to cholangiolitic cirrhosis. The end stages of this type of cirrhosis do not differ from the ordinary atrophic or portal cirrhosis.

Snell (25) of the Mayo Clinic reviews some of the evidence in asking, "Do the residues of viral hepatitis lay the groundwork for cirrhosis?" He feels that full consideration must be given to the possibility that viral hepatitis may lay the groundwork for cirrhosis, if it does not actually cause it.

There appears, then, to be a good deal of evidence that some cases of cirrhosis may be directly or indirectly caused by viral hepatitis. While an absolute answer does not seem possible at present, the case for the affirmative answer is quite strong and prevails in many reputable centers of medical research.

SUMMARY

In summary, this critique has attempted to review the evidence of the occurrence of sequelae of acute viral hepatitis. Chronic disability does occur for periods of time not yet clearly defined as to duration and may occur as a continuation of the acute attack or after presumable recovery from the acute attack. The prognosis can not be definitely answered at present. The percentage of acute cases having chronic disability is small, but no definite numbers can be stated with assurance. That a still smaller group of the acute cases may terminate in cirrhosis seems supported by adequate evidence. Whether the group having chronic disability (the chronic hepatitis syndrome) or what percentage of it goes on to cirrhosis can not be answered at present.

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Present Fundamentals of Some Liver Function Tests

By

C. A. A. SCHRUMPF, M.D.

PORSGRUNN, NORWAY

IT MUST BE EMPHASIZED that every liver function test is only of supplemental nature and should be evaluated in close correspondence with results of the case history and results of the clinical examination. This is so much more important as the liver has many functions which may be involved more and less, or in a very selective way. There exist in other words no liver function test, but a series of partial tests, each of which is related to some specific function of the liver.

CHROMAGOGOUS FUNCTION

One important function of the liver is to produce and excrete bile. Investigation of the serum bilirubin level and examination of the duodenal content

for bile is of distinct value for diagnosis and differential diagnosis of jaundice. The same holds true for tests based on introduction of dye stuffs which are supposed to be almost exclusively eliminated by the liver with the bile. The limitation of conclusions which may be drawn from such tests must, however, be clearly understood. To illustrate this, let me refer to figure 1, 2, 3 and 4.

Fig. 1. tends to illustrate the normal function of a liver lobule with a central biliary channel lined by normal liver cells and again limited from the capillary vessels by Kupffer cells.

Fig. 2. tends to illustrate the condition when these cells are affected which lie close to the portal area. The degenerated cells permit the passage of bile produced by almost the whole lobule into the blood capillaries. Intensive icterus is the result, whereas the

From the Medical Department of the St. Joseph's Hospital, Porsgrunn, Norway.

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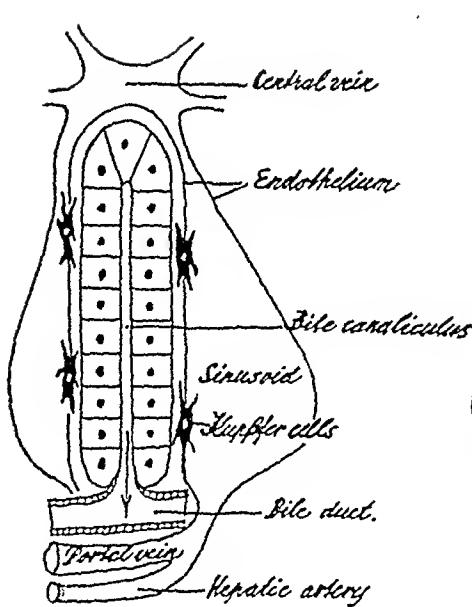


Fig. 1. — Schematic illustration of an intact liver lobule with a central bile canaliculus surrounded by tubular glands, the double blood supply and the Kupffer cells which lie along the portal vascular capillaries. The bile is emptied in one direction into a bile duct, whereas the blood flows in the opposite direction towards the central vein.

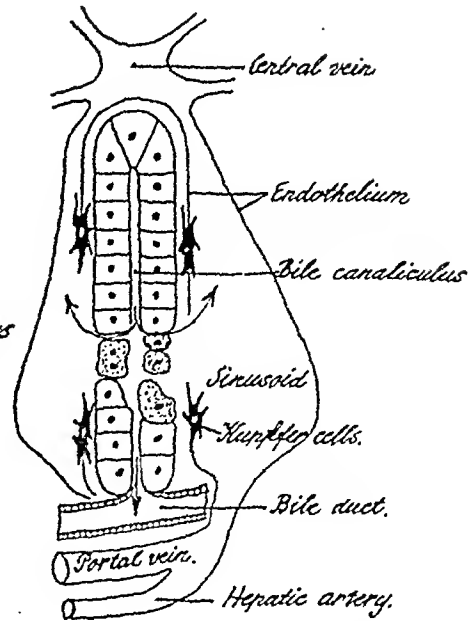


Fig. 2. — Toxic or infectious hepatitis where the cells situated close to the portal area are involved which makes it possible for the bile to pass into the blood capillaries. Most of the hepatic tissue, however, is intact. The result is severe icterus, whereas the parenchymatous lesion is far from extensive. Benign hepatitis.

parenchymatous lesion is far from extensive. Thereby is created what in French clinics is called: "Grand ictère, petite maladie."

Fig. 3. illustrates the condition of a centrolobular affection. Icterus is here less pronounced, in spite of a rather severe affection of liver tissue synonymous with: "Petit ictère, grande maladie."

Fig. 4. tends to illustrate the severity of affection which is characteristic in icterus gravis or acute liver atrophy. Little bile is produced due to the extensive cellular degeneration so icterus is not pronounced in spite of the very severe liver parenchymal lesion.

It is further easily understood that occlusion icterus by stone is a high grade icterus, but evidently not synonymous with a serious damage of liver cells and their functions. Some damage may, however, arise from mechanic obstruction of long standing.

These examples should clearly demonstrate how easily false conclusions may be drawn from estimation of bilirubin index alone. As is evident, a high grade icterus of short standing is usually not indicative of serious hepatic damage, whereas moderate icterus of long standing generally is.

Of great practical importance is the fact, which is relevant from what has been described above, that every type of liver function test based on the elimination of dye stuffs by the liver through the bile has a somewhat limited value. In cases of acute, non-

infectious bile occlusion a high retention of bromsulphalein is not indicative of reduced liver function. The latter may on the contrary be completely normal. Common to all liver function tests based on use of dye stuffs is the necessity of eliminating the possibility of mechanical bile obstruction before positive conclusions are allowed. But even then it is not permitted to regard high dye retention as synonymous with highly reduced hepatic function and vice versa. Here precisely the same considerations hold true which have been related earlier. It must further be kept in mind that no conclusions may be drawn with regard to cholecystopathy in cases of hepatitis or parenchymatous lesion of the liver after administration of tetraiodophenolphthalein in cholecystography. In conditions with or without icterus but with pathologic bromsulphalein retention there will not be eliminated enough dye into the gall bladder to make the latter visible. Much confusion and misinterpreting of results has been occasioned through misconception of this point.

HYMANS V. D. BERGH TEST

Much work and paper has been wasted on the direct and indirect diazo reaction which according to our experience is without much value in differential diagnostic work in connection with jaundice.

The same holds true for qualitative and quantitative determination of urobilinogen and urobiline. Their value is often overestimated. What has been

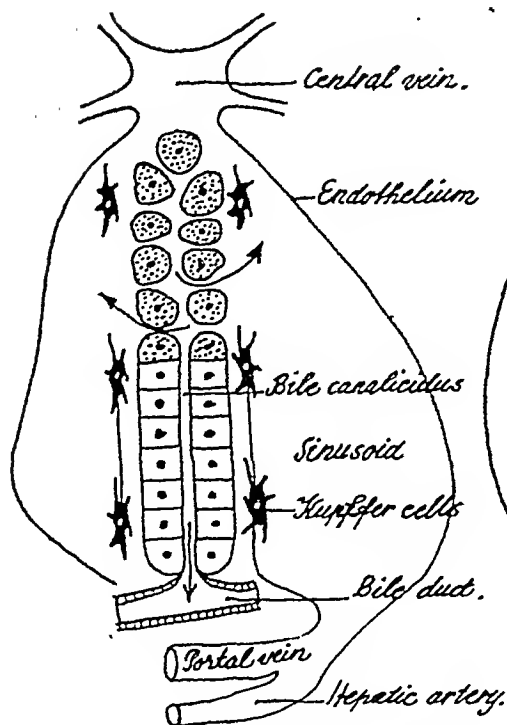


Fig. 3. — The degenerative lesion predominates in the center of the lobule. Icterus is therefore less pronounced, but the parenchymatous lesion is pronounced

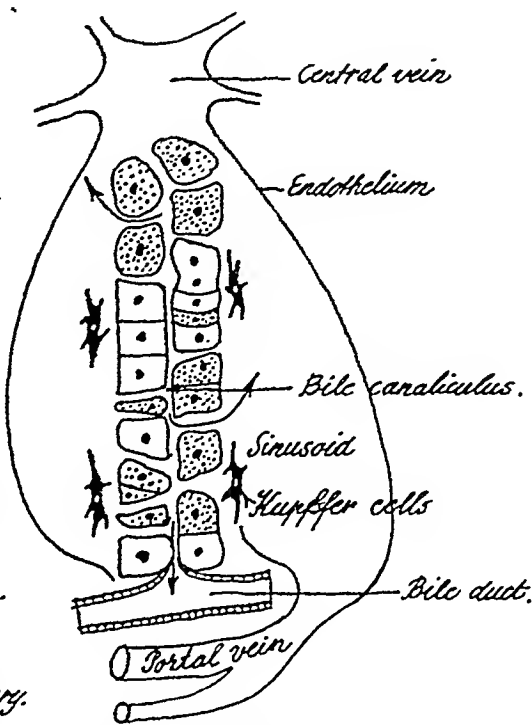


Fig. 4. — There is almost complete, diffuse degeneration of the whole lobule. Little bile is produced and the parenchymatous lesion is heavy. The picture corresponds to the clinical condition of icterus gravis.

said about the diagnostic importance of icterus should be kept in mind during every effort to evaluate the diagnostic possibilities of these derivatives closely related to bilirubin. High concentrations of urobilinogen in the urine are only significant of hepatocellular damage in absence of bile obstruction or hemolytic conditions. Besides, there is one source of error connected with quantitative determination of urobilinogen which usually is neglected. Urobilinogen is oxidized to urobilin very fast in urines containing *escherichia coli*, as soon as nitrate is reduced to nitrite.

METABOLIC FUNCTION: CARBOHYDRATES

Removal of the liver in animals is accompanied by distinct and progressive hypoglycemia. Death will follow unless dextrose is introduced. Ingested monosaccharides are rapidly absorbed from the intestine. The ratio of the rates of absorption of galactose, glucose and fructose being respectively 110, 100 and 43 (Cori). Under normal conditions these monosaccharides are converted into glycogen by the liver, most easily glucose, whereas galactose if given in excess of the liver's immediate capacity, will pass into the general circulation and be eliminated by the kidneys. Other tissue (muscle etc.) seem to have some, but not very pronounced ability to deal with galactose.

About 40 gms. of galactose is the maximum dose, independent of sex, age and body weight. The highest amount excreted in the urine during four hours after ingestion of 40 gms. galactose in 400 ml. water is

not more than one to two gm. Higher values are indicative of reduced assimilative power of the liver and values above three gms. are certainly abnormal. Distinct pathologic results are usually found in cases of hepatitis of some severity.

COMBINED GALACTOSE-GELATINE TEST

It is further known that if the galactose test is performed with simultaneous administration of glucose, the excretion of galactose is markedly lowered, probably due to augmented oxidation of monosaccharides (Fiessinger and Schrumpf). A similar phenomenon has been observed after combined administration of galactose and amino-acids and galactose and fat. The opinion has been set forth that this phenomenon is due to reduced absorption of galactose. It is, however, improbable, that a test of this kind represents any strain on the high absorptive power of the intestinal mucosa. Moreover, it is clearly seen from the blood sugar curves after combined galactose-gelatin administration, that fairly large amounts of galactose have been absorbed during the first hour after the test. Furthermore the same phenomenon is observed if one of the sugars is given intravenously (Stenstam).

Of considerable interest for clinical work is the fact that this phenomenon of interference in connection with combined galactose tests may be missed in certain cases of liver disease, such as liver cirrhosis and liver stasis, because it is so slight.

It seems therefore natural to base our galactose

tolerance test upon these facts in our endeavour to introduce modifications which simplify the test.

The technique recommended for use is to administer 40 gm. galactose together with 50 gm. gelatine. The gelatine must be dissolved in warm water beforehand, cooled and thereafter some lemon juice and the galactose are added. No food is allowed overnight or at breakfast, and the subject empties the bladder beforehand. Blood sugar determinations are made before and one and two hours after the test is started. The urine is collected during the first four hours, and the following 20 hours and the specimens are tested qualitatively for sugar. Performed on healthy subjects there will be no galactosuria and the blood sugar curve presents only slight changes as will be seen in table I.

TABLE I.

Results of the galactose-gelatine tolerance test in 10 healthy subjects.

	Blood sugar before	After 1 hour	After 2 hours	Galactose Urea
1)	101	102	104	0
2)	99	114	112	0
3)	112	119	90	0
4)	105	110	107	0
5)	108	106	103	0
6)	97	101	104	0
7)	102	110	99	0
8)	97	97	109	0
9)	99	102	106	0
10)	99	104	103	0

As will be evident, this procedure means a great clinical simplification of the traditional galactose test. Usually only a qualitative test for sugar is necessary, but if meticulous precision is desired a quantitative determination may be made. This may be of value in certain cases repeatedly examined for progress. The blood sugar determinations will help to make the test more significant during these conditions but they are hardly necessary in clinical work (16).

The galactose-gelatine test has been extensively used for years and has proved to be the most valuable, practical and reliable test for estimation of the liver's carbohydrate function. As usual the laboratory result can only be interpreted in the light of clinical evidence. Table II shows some results obtained by this test. As will be evident, a positive result is only obtained when the liver-cell damage is severe enough. To make this clear, let me show the results of the test performed at different times during a typical case of hepatitis (Table III). As will be seen, there is a gradual return to physiological conditions both with regard to the blood sugar rise and the excretion of galactose in the urine.

It has been shown that rapid intravenous adminis-

TABLE II.

Results of the combined galactose-gelatine test in different conditions.

	Negative	Positive
Acute hepatitis	3	9
Chronic hepatitis	0	3
Neosphenarmline icterus	0	1
Liver cirrhosis	1	4
Pyelophlebosclerosis	0	1
Cholecystitis	0	1
Cholelithiasis	4	2
Cardiac failure	8	6
Anemia and leucemia	4	0
Thyreotoxicosis	3	0
Spleno and hepatomegaly	1	1
Duodenal ulcer, colitis, gastritis, pyelitis	5	1
Cancer of the liver	1	0
Hemolytic icterus	2	0

tration of galactose may give fairly good evidence as to liver impairment. What has to be noted is: The maximum of galactosuria, the time of its onset and, finally, its duration. With a dose of 0.42 gms. galactose per minute for two hours, the curve in healthy subjects is of plateau type and the rate of elimination from the blood in subjects with hepatic disease amounts to one third of the rate in normal subjects. With a single intravenous dose of one cc. of a 50 per cent solution of galactose per Kilogram of body weight, there is less than 20 mg. of galactose per hundred cubic centimeters in the blood after seventy-five minutes in obstructive jaundice and more than this amount in parenchymatous jaundice (1).

TABLE III.

Diagnosis	Date	Bloodsugar fasting	After 1 hour	After 2 hours	Galactose Urea
Hepatitis	27/2.	101	141	105	0.58 g
	7/4.	99	124	92	traces
	9/5.	97	100	84	0

Bromsulphalein test 12th of March: 45 per cent after five min., 0 per cent after 30 min.

So far, these tests have been devised in such a manner as to give a fairly accurate picture of the galactose metabolism in man but they are, however, somewhat complicated, as quantitative determination of blood galactose is necessary (26).

DETOXIFICATION FUNCTION OF THE LIVER

Hippuric Acid Test

The hippuric acid test depends on the observation that benzoic acid given intravenously or orally is conjugated with glycine and excreted as hippuric acid by the kidney. This conjugation takes place both

in the liver and in the kidney, but glycine formation is a process exclusively connected with the liver. The hippuric acid test requires good renal function.

As the traditional use of six gms. sodium benzoate is apt to inflict nausea and vomiting, a modification with use of only four gms. has been introduced. Normally about three gms. hippuric acid expressed as benzoic acid is eliminated in four hours with a variation (owing to the size of the individual) of from 85 to 110 per cent of this amount (13).

The intravenous hippuric acid test is more complicated and so sensitive that it seems unsuitable for differentiation between hepatitis and obstructive jaundice.

Serum Iron Content

In the great majority of cases of acute hepatitis, serum iron values are throughout the illness found to be higher than in cases of jaundice of other origin. A value above 200 gamma per 100 cc. is assumed to be indicative of hepatitis (2).

Takata and Cephalin Cholesterol Reaction

Both reactions are usually positive in hepatic cirrhosis and are transitorily positive in acute hepatitis. The Takata reaction is preferred because it is simple and easy to perform and evaluate (9).

Thymol Turbidity Reaction of Serum

In the great majority of cases of obstructive jaundice this test is negative (18). In hepatitis it is positive in about 90 per cent of cases. Usually the results obtained by this test closely follow the results obtained by the citric acid determination in the blood. In acute hepatitis, however, the thymol test may still be negative when there already is a marked rise of the citric acid level. During convalescence the thymol test usually presents a gradual decrease from initial high thymol turbidity to results in the normal range, when the citric acid level in the blood has already attained a normal value. The thymol test is usually positive in liver cirrhosis, but may be negative when the Takata reaction is positive. Neither this test nor the Takata reaction is specific for liver disease. There is some evidence to indicate that the thymol turbidity reaction may be due to release of an abnormal globulin into the blood stream.

MISCELLANEOUS TESTS

Serum Citric Acid and Phosphatase

From determination of the citric acid and phosphatase level (3) in jaundiced patients, diagnostic conclusions of considerable value may be drawn (11). Usually the citric acid level is distinctly higher than normal in hepatitis. The same holds true for the phosphatase level in obstructive jaundice. The differential diagnostic possibilities are summarized in table IV.

The diagnosis of hepatitis is strongly supported by a high citric acid level in combination with a normal

TABLE IV.

Citric acid and phosphatase level in jaundice

Type of Liver Affection	Serum Citric Acid	Serum Phosphatase
Hepatitis	Above 30 gamma per cc.	Normal or slightly increased
Obstructive Jaundice	Beyond 28 gamma per cc.	Above 20 Units
Partial Bile Obstruction	Normal	10 to 20 Units or more

phosphatase level. False diagnostic conclusions exclusively based on these laboratory data will most easily be made in the group of partial bile obstruction.

HEMATOLOGICAL FINDINGS IN LIVER DISEASE

Prothrombin Level

Maintenance of a normal prothrombin level in the plasma is one important function of the liver. This function is based on the presence of K-vitamin in the intestine and its subsequent absorption. The latter process can only take place as long as bile acid is excreted. A reduction of the prothrombin index below 80 is significative of a lowered K-vitamin content. On the other hand a rise of the blood prothrombin level during 24 hours after administration of two mg. vitamin K is not pronounced or practically absent in parenchymatous affections of the liver (7). In cases of obstructive jaundice the blood prothrombin level will usually amount to more than 20 per cent of the initial level. An affection of liver parenchyma can therefore practically be excluded through performance of this test.

Blood Examination

Macrocytosis and increased diameter of the erythrocytes is frequently observed in diseases of the liver associated with jaundice. It is rather astounding that disturbances with regard to the erythrocyte maturing factor are hardly observed in liver disease. On the other hand usual liver function tests are completely negative in pernicious anemia.

In liver cirrhosis there is usually anemia with hyperplasia of the sternal marrow. Myelopoiesis usually shows no shift to the left in this disease. In hepatitis, however, there is a nuclear shift to the left in the sternal marrow. Dogmatic conclusions are never justified from these findings, as inflammatory processes may distort the typical picture of liver cirrhosis. In several cases of cirrhosis, leukopenia and thrombopenia may occur, significative of a rather dubious prognosis.

The sedimentation rate is usually normal or only slightly elevated during the acute stage of hepatitis. Considerable increase is usually observed during the later course of the disease and during convalescence.

Strictly speaking these hematological findings are not tests of liver function, but they may give helpful confirmatory suggestions in doubtful cases. Throm-

bopenia may have decisive practical importance in the often very difficult differentiation between cirrhotic liver processes and occlusive bile duct carcinoma.

COMMENT

It is well to bear in mind that the evaluation of liver function tests is only possible with an intimate knowledge of the fundamental principles of their mechanism and a realistic comprehension of their possibilities. Every deduction based on these results must be closely related to data from case history and physical examination.

What has to be considered is: Which test, or which tests can be recommended as giving the best information for clinical use? Manifest as liver function is, one single test must obviously fail to give the answer needed. According to our own experience no schemata for investigation of liver function can be complete without the galactose tolerance test. Used in combination with gelatine as outlined above, this test is simple and reliable. It is very useful for differentiation between parenchymatous jaundice and obstructive jaundice. The bromsulfalein test should likewise be used routinely, but the limits of the test must be clearly understood. The same holds true for the determination of the icterus index which has a certain diagnostic value, but is less important from a functional point of view. It must be clearly emphasized that there may exist parenchymatous affection without jaundice and that the intensity of jaundice may diminish in spite of the increasing severity of the condition. In this connection it may be important to stress the occurrence of a functional liver impairment in ulcer without icterus, which frequently has been confirmed by results obtained from the galactose tolerance test. Supplemental valuable information may be obtained from use of the hippuric acid test, the citric

acid and phosphatase test, from the prothrombin level, the Takata test and some hematological findings. As a routine procedure I would recommend the galactose-gelatine test, the Takata test, the bromsulfalein test, icterus index, determination of the prothrombin level and a leukocyte and differential count. The other tests may be reserved for certain doubtful cases.

CONCLUSIONS

1. No single liver function test exists but a series of partial tests.

2. A high grade icterus is usually not indicative of serious hepatic damage, whereas moderate icterus of long standing generally is.

3. Tests based on elimination of bromsulfalein and similar dye stuffs are of no use in parenchymatous affections unless obstructive jaundice can be eliminated. On the other hand cholecystography is dependent on a normal excretory power of the liver cells.

4. The direct and indirect diazo reaction of H. v. d. Bergh is without much value for the differentiation of icterus.

5. Every testing of liver function should include the galactose tolerance test. A practical modification of this test with simultaneous peroral administration of gelatine is outlined.

6. Supplemental information can be obtained from use of the bromsulfalein test, the hippuric acid test, the citric acid and phosphatase test, from the prothrombin level, the Takata test and some hematological findings.

7. As a routine procedure the galactose-gelatine test, the bromsulfalein test, icterus index, the Takata test, determination of the prothrombin level and a leukocyte and differential count are recommended. The other tests may be used if necessary.

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Case Reports from Soper-Joslyn Clinic

By

HORACE W. SOPER, M.D.

and

HAROLD L. JOSLYN, M.D.

St. Louis, Mo.

CASE NO. 1.

PATIENT AGED 44, CLERK. Came under observation October 2, 1947. He complained of stomach trouble, dyspnoea on exertion, nausea and occasional diarrhea and vomiting.

X-ray of the gastro-intestinal tract did not reveal the presence of any lesion in the stomach, duodenum, or small intestine. The colon was redundant in character. Stomach contents after Ewald-Boas test breakfast revealed free HCl 30°, total acidity 60°. Feces analysis was negative for occult blood, but showed an excess of mucus; microscopically, pus cells, striated muscle fibers, fat globules and considerable undigested starch.

Wassermann and Kahn negative. Hemoglobin 97%; red cells 4,910,000; leucocytes 5,800. Differential was well within normal limits.

He made some response to dietetic treatment, but continued to have curious attacks of abdominal pains with occasional diarrhea; however, as a rule, he was constipated.

On November 1 we were able to detect extensive peristalsis on palpation, evidently the small intestine. On November 3, palpation disclosed a mass in the right iliac which had moved and was somewhat tender to pressure, was elongated about four inches in length. The next day and throughout the week thereafter this mass could be palpated on both sides of the abdomen. The feces continued to remain free from occult blood, daily tests were made.

We finally decided upon surgical procedure and he was operated upon by Dr. Dean Sauer on November 17, 1947. Dr. Sauer found a mass in the distal portion of the ileum. The mass extended proximally for a distance of about six inches and distally for an equivalent distance, terminating in the ileum about fifteen inches above the ileocolic valve. It was obviously a chronic intussusception. There was marked fibrosis and edema of the mesentery of the bowel and hypertrophy and dilatation of the bowel above and below the intussusception. The entire mass was resected and, in all, about thirty inches of the distal ileum was removed. End to end anastomosis restored ileal continuity.

He made a very rapid recovery and gained 10 pounds since the operation.

Our original diagnosis was chronic *catarrhal enteritis* which was of several months' duration and not associated with achylia gastrica which is almost always present in cases of catarrhal enteritis.

A review of the literature of chronic intussusception reveals that seven days is the average length of time for it to exist; our case was at least 30 days' duration and it was remarkable for negative X-ray findings and negative occult blood reaction in the feces (Fig. No. 1).

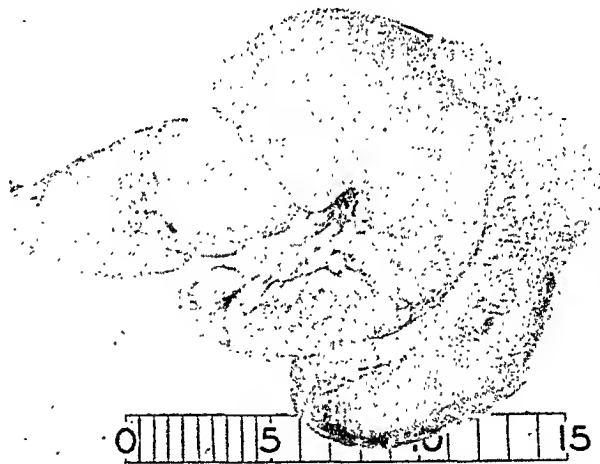


Fig. 1. — A photograph of the excised mass showing the intussusception.

CASE NO. 2

Patient, aged 78, had been under observation for many years for atherosclerosis and hypertension. On a low cholesterol diet and care her blood pressure remained under good control, usually oscillating between 160/100 and 130/90. She was subthyroid and had a tendency to obesity. Finally, she reported to the office January 19, 1948, complaining of dyspnoea on exertion and feeling a pressure and heaviness in the chest. She said she "felt like a friend of mine who recently had died of aneurysm of the aorta." We had X-ray of the chest immediately and, sure enough, the aneurysm was present.

This case illustrates the fact that we should listen attentively to our patients' complaints.



Fig. 2. — Aneurysm of the aorta.

CASE NO. 3

Patient, aged 34, came under observation November 3, 1947. He gave a history of having had ulcer of the stomach and operation of resection of stomach and gastro-enterostomy two years ago. Our X-rays showed deformed stomach and prepyloric perforating ulcer. Feces were positive for occult blood.

He responded very well to dietetic treatment and when he reported to the office January 7, 1948, he had gained eleven pounds. He had very slight discomfort in the stomach and no occult blood. We were under the impression that the ulcer was healing. However, two days later he had severe pains and vomiting which persisted until finally he was sent to the hospital and was operated upon by Dr. Dean Sauer on January 17, 1948. There was a large ulcer on the posterior surface of the stomach the size of one's hand. The ulcer had perforated and the posterior wall of the stomach was formed by the underlying pancreas with its overlying peritoneum. There was a tremendous amount of edema in the hepatogastric omentum and also in the pancreas itself. Multiple nodes were encountered in the gastrocolic omentum adjacent the perforating inflammatory tumor mass. Gastrectomy was performed and microscopical examination of the mass revealed reticulum cell type of *lymphosarcoma*.

Postoperative course was steadily downward and he expired on January 27, 1948 (Fig. No. 3).

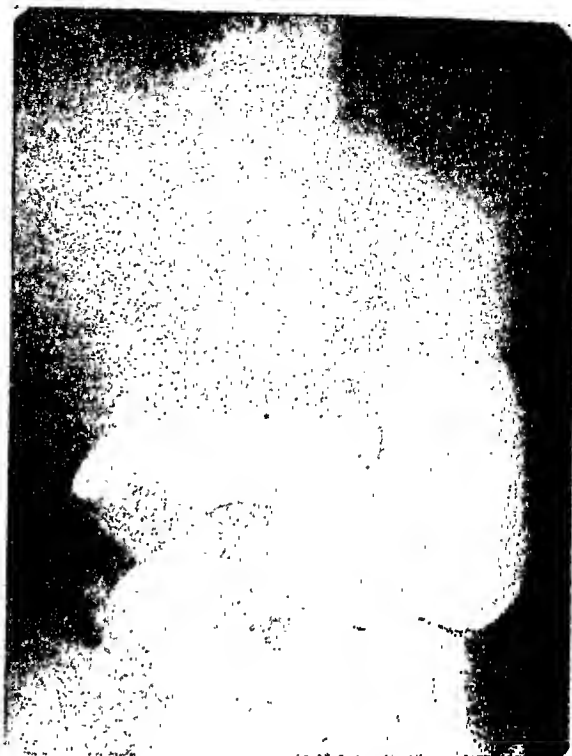


Fig. 3. — Deformity of the stomach with perforating prepyloric ulcer and final sarcoma.

CASE NO. 4

Patient, 38 year old white male, came into the office December 10, 1947, complaining of diarrhea, abdominal cramps, and occasional blood and mucus in the stools. These symptoms had begun rather abruptly two years previously and had persisted until the present time. There had been a weight loss of 30 pounds during this period. He had consulted several good clinicians and had thorough X-ray and laboratory studies. Numerous stool examinations had been negative for *Entamoeba Histolytica* and specific stool cultures for amoeba had been negative. He had been diagnosed as catarrhal colitis and his treatment has consisted of bismuth preparations, phenobarbital and low residue diets.

When he came into the office on December 10, 1947, physical examination was essentially negative. His weight was 166 pounds. Sigmoidoscopic examination showed the rectal and sigmoid mucosa to be injected but no ulceration was present. Blood studies were within normal limits. The Kahn test was negative. Routine examination of one swab specimen and one stool specimen were negative for amoeba and other parasites. The stool specimen revealed 4-plus occult blood. A barium enema showed a twelve centimeter segment of descending colon to be somewhat narrowed and lacking haustration suggestive of an ulcerative process.

In spite of his numerous negative tests for amoeba

he was given a therapeutic trial of emetine hydrochloride. One grain was daily injected for six consecutive days beginning December 17, 1947. Nothing else was changed in his habits, diet, or medication. There was no definite change in his condition the first few days, but on the fifth day he stated he definitely was better. His cramping had ceased and his bowel movements were becoming formed. Following his

emetine, he was given carborsone capsules three times daily until 21 had been taken. By January 6, 1948, he was completely free of symptoms, he had a normal bowel movement each day and his weight had increased to 171 pounds. He was seen on January 20, 1948, at which time his weight had increased to 173 pounds, he was symptom free and on a full diet, including raw vegetables and fruits, for the first time in two years.

Acute Coronary Thrombosis Occurring in a Case of Perforating Lesser Curvature Ulcer, Undergoing Malignant Changes

By

E. MILTON SACHS, M.D.

NEW YORK, N. Y.

INTRODUCTION

CORONARY THROMBOSIS occurring in association with peptic ulcer has not been frequently discussed in the literature. While it is known that the conditions may co-exist, there is a divergence of opinion as to whether there is a relationship between them. In a post-mortem statistical series, Walsh, Bland, Taquini and White (1) noted that peptic ulcer occurred in but five per cent of the 576 patients with coronary disease, and with equal frequency (5.5 per cent) among 1,222 patients without coronary disease, thus emphasizing the lack of association between ulcer and coronary disease. On the other hand, Boas and Levy (2, 3) contended in their review of cases of peptic ulcer and angina pectoris, or coronary thrombosis that a "constitutionally determined heightening of tone and excitability in the vagus nerve seems to be responsible for simultaneous dysfunction of both the stomach and the heart." The small percentage of cases of peptic ulcer in association with coronary disease, as mentioned in the survey of Walsh et al. (1) would seem to preclude the interrelationship between the two lesions, although clinically it cannot be denied that the syndrome of angina pectoris is considerably heightened in frequency and intensity when it co-exists with pylorospasm brought on by ulcer.

The case we wish to report presents many diversified clinical points of interest, especially that of differential diagnosis and the mode of treatment at a time when quick decision was indicated so as to safeguard the life of the individual. The complexity of the problem arose when an acute episode of coronary thrombosis intervened in a case of chronic penetrating lesser curvature ulcer during the stage of acute exacerbation, when the gastric pain per se was

intense, and had always manifested itself by reference of the pain to the precordium. The patient presented all the symptoms of shock. The abdomen was tender and tense, pointing to the presence of an acute perforated lesion. Under such circumstances the diagnosis may be very confusing and the cardiac accident entirely overlooked.

CASE REPORT

J. I., a fifty year old white male, a grocer, first came under our observation on December 20, 1945. He gave a long standing history, dating back over sixteen years, of having had intermittent attacks of upper abdominal pain associated with vomiting usually occurring soon after meals. Repeated X-ray studies during these years somehow failed to reveal the ulcer lesion. (Several X-rays in the possession of the patient taken in the past revealed a smooth lesser curvature and normal morphology of the duodenum). The symptoms would recur and subside at varying intervals with periods of remission sometimes as long as a year or more.

When seen by us during a period of recrudescence, the pain was located in the epigastrium and radiated to the left of the abdomen and upward toward the left chest. His pain came on about one hour after meals, at which time he often vomited. Roentgen studies revealed for the first time a thinly visualized niche about 3/4 of an inch in diameter located on the lesser curvature midway between the cardiac orifice and incisura angularis (Figure 1). On fluoroscope examination, there was tenderness of the abdomen in the left hypochondrium corresponding to the location of the niche. Gastric analysis showed a free acidity of 46 with a total acidity of 64. The patient was placed on a strict ulcer regime which brought about a cessation of his symptoms within a short period of time and enabled him to return to his regular occupation.

The patient remained well this time for only two months, when his ulcer symptoms again returned. The pains had now increased in intensity, assuming a pattern similar to former attacks, particularly regarding the reference of the pain to the precordium. The response to treatment was also less favorable. Suddenly, on the morning of March 8, 1946, he was seized with a severe pain in his epigastrium and precordium which was out of proportion to



Fig. 1. — Dec. 20, 1945 Small niche thinly visualized on lesser curvature of stomach.

his previous attacks. Examination revealed an acutely ill, anxious patient in a semi-recumbent position. He was bathed in cold perspiration and was supporting his upper abdomen and chest because of the acute pain. He was retching continuously and appeared to be in shock. His pulse was rapid, rate 116. Heart sounds were normal. Blood pressure 120 systolic and 80 diastolic. Laboratory studies showed the white cell count to be 16,000 with 75% polymorphonuclear leucocytes; the hemoglobin was 14 gm; the red cell count 4,000,000, Urinalysis was negative.

In view of the long standing history of gastric ulcer, the positive X-ray evidence of a niche and the acute episode of pain and shock, the most likely opinion could lead to no other diagnosis than that of a perforated gastric ulcer with indications for immediate surgery. However, close study of the patient and repeated physical examination of the abdomen failed to reveal absence of liver dullness, nor was there any acute shoulder pain so commonly found with free air in the peritoneal cavity. The likelihood of an acute coronary thrombosis was then considered as the possible cause of the acute pain and shock. An electrocardiographic examination was carried out which established the diagnosis of an acute coronary occlusion with anterior wall myocardial infarction. There were inverted T waves and RS-T elevations in leads I and IV and Q waves in both these leads (Figure 2).

The pain was constant and repeated sedation had to be administered to give him relief. The next day his temperature rose to 103 F. and fluctuated between 101 and 103 F. for five days before returning to normal. Sedimentation rate was 28 mm. in one hour. The patient was kept in bed for a period of six weeks, during which time the acuteness of the pain subsided; residual gastric symptoms, however, were still present. During the following month, the patient showed no signs of improvement — his gastric symptoms persisted, he was losing weight and

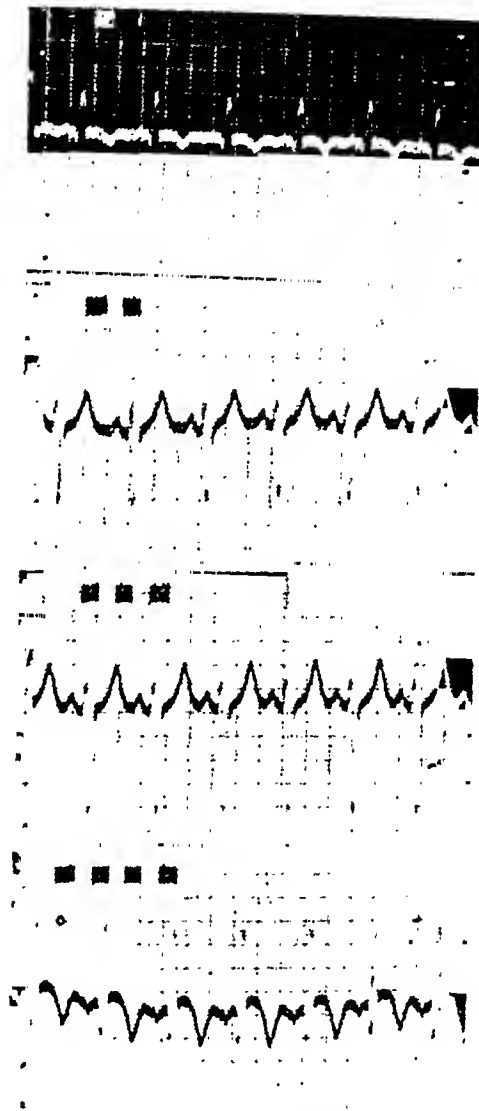


Fig. 2. — March 8, 1945 ECG showing acute coronary occlusion with anterior wall myocardial infarction.

it became more difficult to maintain his nutrition. A re-examination at this time, June 25, 1946, revealed the niche to have grown considerably in size, suggesting the possibility of malignant change (Figure 3). The progressive nature of the lesion and the persistence of gastric symptoms could have led to no other interpretation. Surgery was therefore advised in spite of the fact that only four months had elapsed since his acute coronary occlusion. The electrocardiogram had remained unchanged.

On July 12, 1946, the patient was operated upon by Dr. Ralph Colp at Doctors Hospital under spinal anesthesia. A penetrating ulcer was found high on the lesser curvature that was sealed off by adhesions to the pancreas. A retrograde subtotal gastrectomy was performed. The pathological diagnosis was: (1) Primary Carcinoma of the Stomach arising in a perforating gastric ulcer; (2) Acute Omental Adenitis.

The following is the detailed pathological report: "There was a perforation 1.25 cm. in size and puckering of the adjacent congested serosa. The ulcer was two cm. in diameter with indurated preulcerous walls. The adjacent mucosa was congested and had lost its rugae. The muscularis appeared gelatinous and the base was necrotic.



Fig. 3. — June 25, 1946 Niche considerably increased in size.

There were several medium sized firm nodes in the omental fat which were uniformly pinkish white on section. Microscopically, the walls of the ulcer were variably lined with granulation tissue, atypical glands with large irregular cells containing hyperchromatic macronuclei and nucleoli, and some normal mucosal glands. The tumor tissue extended down into the muscularis. The omental lymph nodes showed a moderate increase in the size of the lymphoid follicles" (Figure 4). The patient

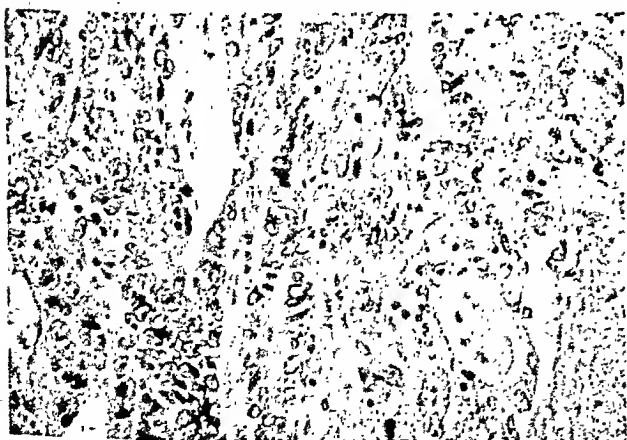


Fig. 4. — July 12, 1946 Specimen showing atypical glands with large irregular cells containing hyperchromatic macronuclei.

made an uneventful recovery and was discharged on the tenth post-operative day. Since the operation he has maintained an excellent state of health. He has been eating well, has been free of complaints referable to his heart or gastrointestinal tract and has gained twenty pounds in weight. X-ray studies one year after operation revealed



Fig. 5. — July 15, 1947 Subtotal gastrectomy. No evidence of recurrence.

a well-functioning stoma without any evidence of recurrence of the lesion (Figure 5).

SUMMARY

Acute coronary occlusion has many times been mistaken for an abdominal catastrophe and conversely, symptoms due to abdominal conditions may simulate those of a cardiac accident. Diagnosis may be even more difficult if in a case of penetrating ulcer with active symptoms, coronary thrombosis supervenes. In such an instance one might erroneously attribute the entire symptom complex to an acute perforation and overlook the coronary thrombosis.

The following points of interest may be repeated in summing up the case:

1. A gastric ulcer may persist for some time without any demonstrable X-ray evidence.
2. When coronary thrombosis occurs in a case of a chronic penetrating lesser curvature ulcer during the stage of an acute exacerbation, diagnosis may be difficult. Electrocardiographic studies should be included along with gastrointestinal studies.
3. In the presence of an increase in the size of a niche the diagnosis of malignancy must be considered and surgery instituted.
4. The occurrence of coronary occlusion with myocardial changes appears to be no contra-indication to major surgery, in the absence of cardiac failure.

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Perforation of the Aorta--A Complication of Carcinoma of the Esophagus*

By

M. C. F. LINDERT, M.D.

and

DONALD WINNIK, M.D.

Wood, Wisconsin

NO MORE DRAMATIC A COMPLICATION of a disease process exists than that of perforation of the aorta during the course of carcinoma of the esophagus. Although penetration into adjacent structures is a frequent complication of esophageal cancer, the secondary rupture of the thoracic aorta is rarely seen and has been infrequently reported.

Review of the literature to date reveals some discrepancy pertaining to the exact number of cases reported. Bockus (1) states that approximately seventy-two cases of perforation into the aorta were recorded prior to 1922. This information was taken from a paper by Schattenburg and Ziskind (2), who in turn relied upon a review by Carr and Hanford (3) for their statistics. In an attempt to clarify these discrepancies one of us (M. C. F. L.) has translated the original work of Knaut (4), which is apparently the first comprehensive review of this catastrophic complication. Out of the series of fifty cases reported there were thirty-two instances in which the thoracic aorta had perforated. Of these thirty-two cases, twenty-eight were secondary to an esophageal malignancy. Carr and Hanford (3) reviewed the literature from the time of Knaut's (4) report until 1922 and found twenty-one cases with perforation into the aorta or great vessels. Of these twenty-one cases, eighteen penetrated the aorta. Schattenburg and Ziskind (2) in 1939 reported one case and remarked that only an occasional case had been added to the literature since 1922. Postoloff and Cannon (5) reported two cases in 1946 and had found six additional cases since the review of Carr and Hanford (3) in 1922, including one case which was overlooked prior to 1922 and reported by Barron. Therefore, upon review of the literature including the report of Postoloff and Cannon (5) there have been fifty-four cases of perforation

of the aorta, due to neoplastic extension from the esophagus.

It is the purpose of this presentation to add three cases.

Case no 1: C. S. Patient was a white male, age 57 years, who was admitted to the hospital on June 5, 1946, complaining of difficulty in swallowing, pain in the chest and the vomiting of food and blood. He had been well until January 1946 when he first noted difficulty in swallowing solid foods. The dysphagia progressed until the time of admission when he could no longer ingest liquids. The pain was severe and localized to the right anterior chest. Attempts at swallowing would result in belching and finally regurgitation. The material regurgitated was observed to contain the recently consumed food and small amounts of bright red blood. He had lost thirty pounds in the five month period from January to June 1946. About two months before admission he became aware of a "lump" in the left side of the neck.

Physical Examination: Upon admission he was found to be a cachectic white male weighing 140 pounds.

Neck: There was a 2 1/2 x 2 1/2 centimeter, firm, non-tender, fixed mass just above the left sternoclavicular joint.

Thorax: The superficial veins of the left anterior chest were prominent.

Chest: No abnormalities of the lungs were noted.

Heart: Rate: was rapid; no other abnormalities.

Blood pressure was normal.

Laryngoscope examination revealed a paralysis of the left hemilarynx.

Laboratory studies showed a hemoglobin of 81% with an erythrocyte count of 3,700,000 and a leukocyte count of 10,000. The urinalysis was normal and the blood serology was negative.

X-ray study of the esophagus with a barium meal revealed a large filling defect in the middle one-third of the esophagus just below the level of the aortic arch.

While being studied and observed, patient had a sudden massive hematemesis of bright red blood. He immediately went into profound shock and expired on June 18, 1946.

Post-Mortem Findings: In the mid portion of the esophagus there was a tumor measuring 10.0 x 7.5 cm. which completely encircled the lumen. In the central

* Veterans Hospital, Wood Wisconsin, and the Marquette University School of Medicine.

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portion of the mass was an erosion of the wall extending to the descending thoracic aorta just beyond the aortic area. Bleeding had occurred through this communication from the aorta into the esophagus, stomach, and intestinal tract. In addition, there was in interstitial hemorrhage which extended posteriorly along the visceral pleura on the left. The tumor extended to the lung, approaching the left main bronchus from the posterior wall. A metastatic node was present in the left cervical region weighing 95 gm. (See Fig. 1, 2).



Fig. 1. — Case No. 1. Carcinoma of the esophagus with perforation of aorta showing site of penetration on the aortic side. Cotton tip in esophagus.

Microscopic: There was considerable necrosis of the peri-aortic adventitial tissue. No actual tumor invasion of the vessel wall was seen. However, there were some changes in the wall of the aorta. The intima was markedly hyalinized and was covered with an irregular coat of polymorphonuclear cells. The tumor of the esophagus was a papillary squamous cell carcinoma, Grade III.

Case no 2: G. P. Patient was a white male, age 58 years, who was admitted to the hospital on November 25, 1940 because of coughing up blood during the past day. He was known to have a carcinoma of the esophagus since October 1939. A gastrostomy had been performed in October 1940. On the day before admission he began to retch and cough up large amounts of bright red blood. This continued until the following day, November 26, 1940, when the patient expired.

Autopsy: done the same day revealed a large lesion of the lower one-third of the esophagus which was covered by a large amount of blood. The esophagus for a distance of eight cm. was completely eroded and was covered by a grayish-brown exudate. There was a communication between the esophagus and the aorta, measuring about six mm. in diameter. (See Figs. 3 and 4).

Microscopic: Multiple sections prepared from the area of esophago-aortic adhesions showed a tumor fixation of



Fig. 2. — Case No. 1. Same as Fig. 1, revealing site of perforation on the esophageal side. Cotton tip in esophagus.

the two structures. There was quite extensive carcinomatous involvement which formed the outline of the esophageal perforation. This infiltrated externally, involving the adventitia of the aorta for a wide area about its perforation. The tumor infiltration was a squamous cell carcinoma. At the margin of the aortic perforation the tumor cell nests were seen in the adventitia and came to the edge of the histologically intact tissue. The substance immediately about the perforation was necrotic fibrin material and necrotic aortic wall. This aortic wall showed a gradual change from a quite average vessel to one of complete necrosis but with very little inflammatory reaction. The



Fig. 3. — Case No. 2. Carcinoma of the esophagus with perforation of aorta showing site of penetration on the aortic side. Cotton tip in esophagus.

aorta distant from the site of perforation showed a few spotty areas of medial cystic necrosis. The appearance was that of an ischemic necrosis of the aortic wall without cellular reaction. The adventitial surface of the aorta showed such an extensive tumor involvement that it was impossible to identify the vasa vasorum.

Case no 3: A. B. This 76 year old white female entered the hospital on August 10, 1933, complaining of an inability to swallow. Three months previous she began having difficulty swallowing solid foods and about two months ago noted that she could only swallow liquids. During the last week before admission she was unable to swallow liquids.

Physical examination was essentially negative except for definite evidence of weight loss. Blood pressure 140/100.

Esophagogram on August 14, 1933 revealed obstruction of the esophagus, distal end of middle third, which was thought to be malignancy.

Esophagoscopy on August 22, 1933 revealed edematous mucosa anterior two-thirds with thick ulcerative membrane posterior one-third of obstructed area in lower one-third of esophagus. This was interpreted as carcinoma.

Gastrostomy done on September 6, 1933 — Patient tolerated surgery well and was treated palliatively and was doing quite well until January 7, 1934 when she complained of pain in the abdomen, coughing and vomiting. On January 22, 1934 at 12:30 A.M. she began to hemorrhage from the mouth. General condition became progressively worse and patient died at 1:25 P.M., approximately thirteen hours after the bleeding began.

Necropsy on the same day as the death revealed the upper portion of the esophagus to be dilated, measuring 5.5 cm., whereas the lower portion measured 2.5 cm. The middle one-third was occluded by a large annular tumor mass, involving the entire circumference of the esophagus and extending toward the right main bronchus. This tumor mass measured 6.5 cm. vertically and 5 cm. horizontally. The tumor had eroded into the hilus region of the right lung and had invaded into the surrounding tissue. The proximal portion of the tumor was an annular ring which had a valve-like arrangement, and beneath the valve there was a necrotic area. This necrosis measured two cm. in diameter. The center of the necrotic area was hemorrhagic, and communicated with the thoracic aorta through a sinus which measured five mm. in diameter. The aorta, in its arch and descending portion, showed diffuse atheromatosis, with calcification, and in the upper portion of the thoracic aorta, just below the arch, was a perforation which communicated with the esophagus.

DISCUSSION

Undoubtedly this complication occurs more frequently than has been reported. Sudden death during the course of esophageal carcinoma should always suggest this method of exodus. Reviewing all the cases of carcinoma of esophagus in two general hospitals we are able to find several examples of this, but in the absence of an autopsy were unable to prove positively the existence of such a process other than in three cases reported.

Postoloff and Cannon (5) revived an interest in the pathogenesis of the aortic penetration. They concluded, after careful study of the site of perforation that, 1) the tumor cells did not invade beyond the adventitia, 2) the vasa vasorum were thrombosed, the thrombi in same being due to tumor, 3) the bacterial



Fig. 4. — Case No. 2. Same as Fig. 3, revealing site of perforation on the esophageal side. Cotton tip in esophagus.

infection did not play a significant role. Unfortunately, many of the case reports do not discuss the microscopic findings. However, in a carefully studied case by Barron (6) in 1916, he pointed out the presence of a rather large amount of inflammation and minimal cancerous infiltration and concluded that the inflammatory process greatly contributed to the final perforation. He cited hypertension and mechanical trauma of food as possible factors.

In two of the three cases reported detailed studies were made of the sites of penetration. Marked necrosis, without inflammatory reaction, was apparent in both. Tumor infiltration beyond the adventitia was not seen. The vasa vasorum were not demonstrable in any of the sections. Nevertheless, it appears exceedingly logical that, in the absence of a penetrating cancer tissue and minimal inflammation and the presence of marked necrosis of the aortic wall, a circulatory disturbance such as thrombosis of the vasa vasorum could be considered as the most salient etiological factor.

SUMMARY

1. Three cases of perforation of the aorta complicating carcinoma of the esophagus are reported.

2. An attempt is made to clarify the statistical data on this subject.

We are indebted to Dr. Joseph M. Lubitz, Chief, Pathologic Service, Veterans Administration Hospital, Wood, Wisconsin, and Dr. Joseph F. Kuzma, Head of the Department of Pathology, Milwaukee County General Hospital, for the pathological findings in the cases reported.

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NUTRITION

Obesity: Psychiatric plus Dietary Approach to Its Treatment

By

ESTHER TUTTLE, M.D.

NEW YORK, N. Y.

OBESITY INVARIABLY IS AN IMBALANCE between energy intake and output, resulting in a storage of inert fat in the body. Obesity adds to the burden of normal physiological functions of the body and thus becomes a menace to good health.

The most important reason to keep a normal weight is to prevent a coronary attack. It is an established fact that fat people get hardening of the arteries earliest. The fat in the bodies of obese people causes an increased amount of fat in the blood stream. This fat is called cholesterol and is determined by tests in the laboratory. This blood fat or cholesterol, when in excess, deposits in little crystals inside the linings of the arteries and remains there until changes take place in it and become calcified. The result is hardening of the arteries in obesity. The establishment of coronary disease follows the same pattern; the calcium that follows the fat crystal deposits into the coronary arteries causes their hardening, and nourishment to the heart cannot get through.

When there is a general deposit of calcium throughout the arterial system in the body, the obese victim tends to develop hypertension. If the obese person will reduce the weight, while there are cholesterol or fat deposits in the arteries and before calcification has taken place, the blood pressure will usually return to normal simultaneously with weight loss. There is some truth in the statement that for each pound of excess weight lost, the blood pressure goes down one point. The presence of fat not only adds to the mechanical burden of the heart, but also predisposes to arterial degeneration, which is of more importance than the high blood pressure.

A second reason for wanting a normal weight is that we might be admired by our fellow man. The beauty establishments will sometimes succeed in reducing weight, where a physician may have failed, due to their play-up to the aesthetic. The patient is often given daily regular exercises and frequently with music accompaniment. This is effective only through

substitution of interest in exercise and the transfer of interest away from food. This procedure keeps the obese person busy even though the actual weight loss comes not from the exercise but from the diet that is supplied.

AN APPROACH TO THE PROBLEM OF OBESITY

With careful psychiatric investigation of the cause for over indulgence in food, a great majority of patients reveal an inability to cope with an environmental stress. This results in a nervous sensitive stomach that gives the patient a feeling of gnawing sensation or quivering weakness which is pacified only with more food. Often a blood sugar determination discloses a low sugar level. Their nerves burn up their sugar; therefore, the nervous appetite demands sweets. Sugar satisfies and calms the hyperactive stomach, but is absorbed quickly and the same vicious cycle repeats with the increasing demand for food.

In the past, some clinicians have used the belladonna group of drugs to control hyperactivity and excessive gastric secretions to check a false appetite. There is a fallacy in such direction of treatment, in that it interferes with nature's production of digestive juices which may cause irreversible damage and stomach trouble.

Where there is a normal secretion of digestive juices, with a normal increase in their flow as a direct response and parallel with the emotional disturbance, why not aim to help that patient's ability to accept life or guide him into a better environment?

DIETARY MANAGEMENT OF OBESE PATIENTS

In planning the diet and any medication required for the treatment of obesity, a first consideration is to determine the causes for the obesity; what is their importance, and how the individual is reacting to his environment. The facilities of the laboratory are utilized for basal metabolism determination, blood chole-

sterol, differential blood count, urea and chloride excretion levels.

The phlegmatic, lazy person who sleeps long and more soundly may be benefited by medication to stimulate the thinking part of the brain. In a small percentage of cases these drugs seem to help to diminish the appetite. The obese patients who do not show a lazy attitude and sleep poorly may acquire a nervous temperament and an inability to cope with an environmental stress. These unhappy, emotionally disturbed people almost invariably suffer with nervous stomachs.

To maintain health while losing weight, it is essential that the actual weight loss must come from the loss of fat and at the same time the tissues that build muscle and the other organs must be well supplied and replaced.

In the management of over 500 cases of obesity, gratifying results have been obtained by curbing the appetite, not by drugs, but with the use of an intact protein combined with carbohydrate.* The intact protein-carbohydrate combination used contained quality proteins of high nutritive and biologic values with all of the essential and non-essential amino acids. Each ounce represented 61.25% of protein derived from milk, milk sugar and aromatic agents. The salt content was negligible and fat content 0.25%. A heaping tablespoonful was equivalent to approximately 16 grams of the material and made available about 55 calories. The intact protein carbohydrate combination solicited patient acceptance because of its pleasant flavor and being in a powdered form, it could be readily suspended in milk or water.

The diet must be calculated so that there are at least 1 1/2 grams of protein per kilo gram of body weight to establish normal. There must be sufficient carbohydrate or sugar to burn up the fat that is being lost. If the carbohydrate is insufficient, after two or three weeks of dieting, acetone will be found in the urine, indicating the patient is ill and has an acidosis. The diet must be arranged suitably to prevent this condition from occurring.

The rationale of treatment is based on the need for proteins to maintain proper cellular integrity, repair of tissues, to promote healthy glandular secretions, to build stronger organs and muscles and maintain normal blood proteins.

It was found that a heaping tablespoonful of the intact protein-carbohydrate combination taken a half-hour before lunch, dinner and at bedtime would "quiet" the stomach apparently as a result of its bulk, and more importantly because proteins remain longer in the stomach, absorbed more slowly and the sense of fullness remains longer. Excessive appetite is satisfied, fatigue is prevented and a controlled planned amount of food is easily managed. In this way,

normal functions are constructively improved and the appetite is gratified.

PSYCHIATRIC MANAGEMENT OF OBESITY

In many patients a plan is followed through the use of a diagram first published by Cahot many years ago. This is a cross with a balance of emotional health when each of the four legs, Love, Worship, Play and Work, are equal. We face the patient's life factually, and where there is a wall that appears unsurmountable, we stop banging the patient's head against it, or bemoaning or weeping over it which, we soon learn, is wholly self-destructive.

We plan with the patient any possible means of breaking this obstacle — of removing it. Often, this can be done with great patience on the part of the physician, plus a willingness of the physician to devote much time and expend a great deal of energy. When an obstacle is apparently unsurmountable, then we learn how best to live with it there, and develop a path in life to by-pass such an obstacle.

There are times when some medication is needed to overcome depression and induce a favorable effect on mood and well-being. The patient must be given a clear insight into his problems, and when needed, such help is given to help him become more active physically and mentally, and more prone to exert self-discipline and will power in eating habits and in following directions of the physician.

DISCUSSION

In the management of obese patients, my gratification comes through teaching the patients to live with complacency within themselves. Environmental obstacles are viewed, removed when possible or accepted with a healthy mind, and whenever possible, new interests are created or developed.

We learn to live today and recognize the futility in lamenting about yesterday, a day always gone and always a past. By concentrating on making today a constructive day we protect tomorrow. We stop looking over the horizon. No one has ever touched a horizon; it is always ahead, unreachable as is tomorrow. Most unhappiness with the disturbed body functions occurs from fear and most fear is not for the moment, but for the time and days we have not yet reached. By controlling our conduct today, we best prepare for tomorrow.

This part of obesity treatment; the removal of obstacles, or the learning to get over or around a hurdle is started after nervous exhaustion is controlled with the pleasant tasting intact protein carbohydrate combination in powder form.

Several cases selected at random are presented showing the control of obesity through adjustment of life today and the improvement in physical health.

Each case had a complete medical survey. Basal metabolism, electrocardiograms, blood cholesterol levels, complete blood counts, urine analysis, gastric

* Supplied as Protinal by The National Drug Company, Philadelphia, Pa.

analysis and X-ray studies. Space will not permit a complete report of the laboratory data.

CASE REPORTS

Case No. 1, Female, age 50, married, first seen 6/22/46.
Chief Complaint: Pain in right heel with inability to walk for two months. Arthritis deformans of both hands. Stiffness in both knees. Pain in both hips, particularly at night. Sleeps poorly. Eats "lots of Candies and Sweets."

Physical Examination: Height 62 inches; weight 200 1/2 lbs., blood pressure taken at beginning of examination and after consultation was 210/110. Internal examination showed senile changes following menopause three years ago.

Treatment: Prescribed a salt-free intact protein-carbohydrate (powdered) combination, one tablespoonful in milk 1/2 hour before lunch, dinner, and bedtime. Management of arthritis through combined obesity diet, relief of anxiety that she would become bedridden; ovarian medication to help in arthritis as well as an aid to better, restful sleep. Short wave therapy; vaccines, attention to bowels, and salicylates for relief of arthritis pain.
Progress: The influence of the treatment on weight and blood pressure is given in the following summary:

Date	Weight	Blood Pressure
6/22/46	200 1/2	210/110
7/2/46	195	178/96
7/17/46	186	152/88
7/31/46	179	142/92
8/14/46	174 3/4	148/84
9/5/46	167	138/80
2/18/47	147 1/2	120/80

On 7/19/46, ovarian medication was ordered taken every other night instead of every night. Internal examination now normal. Arthritis less painful to the extent the patient can now use his to get to office.

On 2/13/47, heart sounds were of good quality, rate was 62. Ovarian medication only twice a week. Patient walked two miles without any apparent discomfort.

The patient was last seen 1/15/48 at which time her weight was 140 3/4, blood pressure 130/88 and she had no complaint. She was instructed to take the intact protein carbohydrate combination before lunch and dinner should any indication of nervousness appear. Sleeps well; walks freely without complaint. She had weighed 137 lbs. which I had instructed her to consider her low level and increase her food intake sufficiently to reach a top morning weight of 140 lbs. Relief of arthritis and blood pressure reduction paralleled the reduction in weight.

Case No. 2, Male, a physician, age 47; first seen 12/3/47.
Chief Complaint: "Acute indigestion." Local physician diagnosed coronary disease. Severe pressure in precordial area.

Physical Examination: Weight 165 3/4 — height 63 1/2 inches. Had so much abdominal distention it was not possible to outline or palpate the liver. Definite osteoarthritis in fingers and knees. Heart sound snapping; murmur at apex. Recognized a nervous response to business anxieties and a wife always nagging and envious of wealth.

An ECG — Shows definite early signs of myocardial damage. B. M. R. (—) 24; blood cholesterol 299; segmented 38%; lymphs 43%.

Treatment: Prescribed a salt-free intact protein carbohydrate combination in milk 1/2 hour before lunch, dinner and bedtime and gave the patient an obesity diet. A mild sedative, thyroid, given to control undue nervous-

ness. Efforts made to relieve him of his anxiety complex.

Progress:

12/3/47	165 3/4
12/13/47	158 3/4
1/17/48	150 1/2
2/21/48	146

On 1/17/48, all medication with exception of B complex was discontinued.

On 2/21/48, the blood cholesterol was 144; no complaints; digestion apparently normal, no fatigue present, daily bowel function. The patient was advised to consider 146 lbs. as low weight, and to increase food intake to gain with top morning weight of 150 lbs.

Examination on 3/20/48, the weight was 144 1/2; the patient felt wonderfully well, having no complaint of arthritis pains, indigestion or fatigue.

Comment: Relief of anginal pain paralleled reduction of blood cholesterol level.

Case No. 3, Female, age 58, — W.

Chief Complaint: Severe headaches, constant heartburn, abdominal pains, indigestion. Not interested in losing weight. Exhaustion from poor sleep.

Previous History: Treated for past 20 years for chronic gall bladder disease, arthritis, anemia and high blood pressure. Thyroidectomy 11 years ago. Has been under medical care on and off for reduction of obesity for 20 years and believes she knows she cannot lose weight.

Examination: X-ray examination of gall bladder showed filling defect of gall bladder but no stasis. ECG showed heart block; B. M. R. + 11 to + 28; blood cholesterol normal; Westergren sedimentation rate 22; hemoglobin persistently low with normal R. B. C.

It was not possible to obtain specimen for gastric analysis, since the mention of this procedure caused a fantastic elevation of her blood pressure with severe headache and vomiting resistant to medication for several days. Empirically, hydrochloric acid was given resulting in an aggravation of the heartburn and soda bicarbonate relieved it. She was placed on frequent protinal feedings.

The cause for exhaustion resulting from poor sleep and fear of sleep due to frightening dreams was determined. She had no relatives and few friends. She has a very highly emotional, excitable husband, completely absorbed in the differential respect and flattery given to an outstanding and successful professional man. She felt outside the needs for his life's pattern. She was alone and fearful that with intensity of work and his excitability he will suddenly die. She lived always "tomorrow and tomorrow was dreaded."

Treatment: With intact protein-carbohydrate combination, high mineral and vitamin diet, the patient's weight in one year dropped to 131 lbs. with blood pressure 134/74.

Discussion: Body functions were restored to a better balance by maintaining a comforting sensation of stomach fullness with Protinal.

At each visit much time was spent teaching her to concentrate on living each minute at a time, and each day at a time. Without mentioning weight loss and obesity, because of her conviction that she cannot lose weight, she steadily lost 40 pounds and in the meantime became intensely interested in her new attractive appearance. Her threshold for pain was raised so that arthritis pain, which in the past, was felt keenly and made her more nervous and eat more sweets followed by indigestion and the vicious cycle of more arthritis, now, was seldom mentioned.

The arthritis was helped by better digestion, loss of weight, interest in her personal attractiveness and much more physical activity that gave better circulation to her joints.

Case No. 4, Female, age 48 -- W.

Chief complaint: Obese since 1925 when she gained 20 pounds in a few months. Dyspnea, palpitation and dizziness are other complaints. Pain in knees and some stiffness in fingers in the morning.

Previous History: Has been taking Thyroid one grain daily for 11 years.

Examination: January 1948; Weight 175 lbs.; Height 64 inches; Blood Pressure 97/62. ECG showed a partial first degree auricular -- ventricular block with prolonged conduction time. Heberden's nodes on fingers. Blood cholesterol 216. Sedimentation Rate 30 Westergren.

Treatment: Psychiatric approach to her emotional problems and getting her cooperative interest along with sufficient thyroid to restore glandular function and proper diet supplemented with protinal resulted in a gratifying response of the patient. Last visit June 1948. Weight 144. B. P. 112/70. Blood cholesterol 132. Sedimentation rate 10 Westergren.

Discussion: The patient's father was a dominating man with a violent temper. The mother was an unintelligent, beautiful woman with a good natured disposition. Self-expression was never permitted in the patient's childhood. She graduated from a leading woman's university. She always had a sense of insecurity and inability to compete. Personality consultations revealed her fear that other people would learn of her unhappy childhood and recognize her own incompetence, so she withdrew from any gainful occupation.

The patient is married to a clear, precisely, thinking successful professional man who expresses admiration for accuracy and beauty. They have two children; one has

her family's emotional pattern. This increases her own nervous tension through guilt, so that she laments at her failure to control her emotional unbalance which she recognizes in this child. This is a case of self-destruction. Emotionally, she was still a child and had never reached adult life. Mentally, she is very keen, intelligent and aware of and concerned by worldly events. She is helpful and befriends those people who come within her sphere of influence. Her childhood emotions conflict, confuse and dominate her conduct, and her natural intelligence is supplanted by her confused early life.

The patient did not accept an existing tangible fact, recognize it, and finding it an obstacle to her happiness, "face it" and plan to remove it. Any obstacle to her was something to bemoan because she had no normal childhood.

We accepted each obstructing idea and enacted on the fact of its existence rather than the reason or the why of its presence. Then, what to do about it! If it was something not removable, we looked for other avenues of interest and concentrated energy on developing manageable interests. Life does not stop at obstacles; we live the day and awaken to another new day. She learned to accept the day's facts, and to close the door of the past for all yesterdays are gone and cannot be re-lived.

These ideas aroused her cooperative interest with energetic enthusiasm and self-confidence. She was helped by compliments received for her attractive figure, and happiness expressed in her face and manners.

SUMMARY

Over 500 patients were treated for obesity with an intact-protein, of high biologic and nutritive value, combined with carbohydrate, rendered palatable by its fine mesh size and excellent flavor. The psychiatric approach to the problem of obesity is also stressed; and the results indicate that the combined therapy tend to yield most gratifying results.

Nutrition Notes

Starvation and Inflation

India, on the very threshold of her new life of liberation, finds that the scientific viewpoint with respect to nutrition is under pressure from several angles. The indigenous systems of medicine, especially Vaidak, maintain respect for concepts which modern medicine discards, and these systems are still influential in the minds of many medical men in India. The first and foremost of the Vaidak tenets is the restoration and fostering of everything indigenous to the soil, and this has gripped the popular imagination partly because the indigenous remedies are cheap. The idea that remedies which are native to the soil will cure diseases occurring in those regions has for us in America today no more than a philosophic attraction, at best.

Secondly, the teachings of Western civilization with respect to nutrition have not, as yet, been thoroughly assimilated and converted into Indian terms. Finally, even where the modern concept of a balanced

diet prevails, it is largely a counsel of perfection rendered sadly inadequate because of the lack of food and the exorbitant inflationary prices demanded for even ordinary nutrients. In many instances there has been a 300 to 500 per cent increase in food costs and, not infrequently, insufficient rationing and profiteering.

In spite of a tragic food situation complicating the political turmoil of recent years, there is evidence of sound medical investigation, and a refreshing tendency on the part of physicians to "think things out for themselves." At the present moment, of course, the vital need is for more food and lower prices.

Pernicious Anemia

Recently Murphy (1) of Australia described a case, obviously one of pernicious anemia in a patient, who, while lacking the intrinsic factor of Castle nevertheless showed a definitely acid gastric secretion. His case, as reported, is a strong challenge to the ancient dictum that achlorhydria is constant and necessary to the diagnosis. Now Benjamin (2) of Brook-

lyn describes an anemia in a female infant, and has followed the case a dozen years. She lacks the intrinsic factor of Castle and also free hydrochloric acid in the gastric juice, but does not always show achlorhydria, and her disease shows no tendency to spontaneous remissions. The disease began at eight or nine months of age. The parenteral use of liver extract is necessary to maintain normal erythropoiesis. It is suggested by Benjamin that the patient may have had a congenital absence of the intrinsic factor, thus distinguishing the disease from the adult form of Addisonian anemia. If this is not so, then the patient probably experienced a sudden loss of the intrinsic factor during the first few weeks of life, but this second hypothesis seems improbable. Since the peripheral blood picture and marrow picture in relapse were indistinguishable from adult pernicious anemia, there seems to be no objection to admitting it to be a case of Addisonian anemia. Therefore, a second ancient dictum, viz., that true pernicious anemia is a disease only of adults, seems to have been successfully challenged.

1. Murphy, A.: True pernicious anemia without achlorhydria. *Med. J. Australia*, April 24, 1948, V. 35, No. 17, 521-530.
2. Benjamin, B.: Infantile form of pernicious (Addisonian) anemia. *Am. J. Dis. Child.*, Feb. 1948, V. 75, No. 2, 143-189.

Are Hormones of Any Use in Treating Obesity?

When an obese patient is definitely hypothyroid, the use of thyroid extract is indicated, and, when properly administered, greatly facilitates reduction in weight. In an obese individual whose basal metabolic rate is normal, the use of thyroid extract usually produces increased appetite, annoying and sometimes dangerous tachycardia but usually no satisfactory weight reduction. What about the use of other available hormones?

The average internist is not a specialist in endocrin-

ology and the reading of books on the subject of the ductless glands is endless, difficult and, too often, confusing. To state that there is a large element of myth in current endocrinology is probably true, since such a statement is equally applicable to every department of medicine. But who has seen a case of pituitary adiposity cured solely by the administration of pituitary extract? Who has seen a case of hypogonadal obesity cured solely by the use of gonadal extracts?

Kunde (1) in a gratifyingly frank manner, in speaking of patients whose adiposity ordinarily is attributed to endocrine dysfunction (other than hypothyroidism), says, "their adiposity seems to be due to some unknown constitutional discrepancy in their metabolism." Kunde does not argue for or against the fine endocrine diagnosis in adiposity. But he shows that adiposity, conforming to the various endocrine patterns can be controlled by diet alone, and without the use of any endocrine product. He uses a diet high in protein (of which the patient may eat all he wishes), low in fat and low in carbohydrate, protected suitably by minerals and vitamins. There is no counting of calories. But there is a frank statement to the patient that the diet must be followed.

Kunde's work seems to be in line with medical thinking during the past decade. At least it is practical. The theorem has been developed and widely disseminated that there is no such thing as *endogenous obesity*, and that all obesity (excepting hypothyroidism) is due to eating too high a caloric diet. Kunde found no ill effects in 50 patients resulting from the very high protein diet. He found that good results were possible without endocrine products, although he used gonad therapy terminally on cases of Frölich syndrome after diet alone had produced marked weight loss.

1. Kunde, M. M.: The role of hormones in obesity. *Ann. Int. Med.*, May 1948, V. 28, No. 5, 971-989.

Abstracts on Nutrition

OSMOND, A. AND CLEMENTS, F. W.: *Goiter studies: II. Relationship of endemic goiter to the food consumption pattern of families.* (*Med. J. Australia*, May 29, 1948, V. 35, No. 22, 665-669).

A food consumption survey by the weekly inventory method was made for 112 households in the East Gippsland district of Victoria, but no relationship was found to exist between the diet of the household and the existence of endemic goiter in the children or the urinary excretion of iodine of school boys.

SLOBODY, L., UNTRACHT, S. AND HERTZMARK, F.: *Rice sensitivity in children.* (*Arch. Ped.*, April 1948, V. 65, No. 4, 183-193).

Positive skin reactions to rice in dermal tests are

extremely infrequent in normal adults and normal children. Although positive dermal reactions to rice occur frequently in "allergic" children (those suffering from asthma, for example), these same children can eat cooked rice with impunity. The authors interpret this finding as indicating that cooking in the presence of moisture denatures the rice.

GOLDBERG, L., KROPMAN, M. AND THORP, J. M.: *A survey of vitamins in African food-stuffs.* (*South African J. Med. Sci.*, 1947, 12, 171-178).

Legumes have been found to exhibit little variation in riboflavin and nicotinic acid content among the different species. Outstanding is the high nicotinic acid content of ground nuts (peanuts), at least a dozen times as high as other species.

MOORE, F. D.: *Surgical nutrition*. (Nutrition Reviews, June 1948, V. 6, No. 6, 161-164).

General emphasis is placed on intracellular metabolism, something which is not coercible by the usual parenteral administration of protein, carbohydrates and fluids, but depends ultimately upon the endocrinology pattern of the individual and the nature of protoplasm itself. Avoidance of salt in the early post-operative phase has done more to ease the early convalescence of patients following major gastrointestinal surgery than any other single development in the past few years. Blood transfusions run the risk of virus hepatitis but concentrated albumin or half-reconstituted dried plasma in acute hypoproteinemic conditions plus planned restriction of water intake are to be preferred over massive plasma or whole blood infusions.

However, in the replacement therapy of shock, whole blood is far superior to plasma. Probably there has been too much worry about negative nitrogen balances following trauma or operation, since it actually appears to do no harm. Yet it is wise to avoid any unnecessary prolongation of the transient post-operative period of starvation. Epochs of evolution have produced an endocrine and chemical response to stress (negative nitrogen balance) which survives despite attempts to bury it under amino acids. Only when the lean body weight increases is fresh protoplasm being formed. We need to know more about intracellular nutrition.

SELLERS, E. A., LUCAS, C. C. AND BEST, C. H.: *The lipotropic factors in experimental cirrhosis*. (Brit. Med. J., June 5, 1948, 1061-1065).

Hepatic cirrhosis of moderate degree, produced in adult rats by carbon tetrachloride administration, resolved remarkably when sufficient pure choline chloride or dL-methionine were given, in addition to the basal hypolipotropic diet. A high protein diet containing an adequate amount of naturally occurring methionine produced equally good recovery. It seems probable that favorable clinical results in cases of liver damage obtained by therapeutic diets may be attributed to the lipotropic factors which the diet supplies.

WEIDEN, S.: *Investigation of carbohydrate metabolism in normal pregnancy*. (Med. J. Australia, May 22, 1948, 646-651).

Symptomless glycosuria was found in 30 per cent of women during early pregnancy and in 20 per cent in later months, the patients being on normal diets. Sixty per cent of pregnant women showed glycosuria after a dose of 50 grams of glucose. A low fasting blood sugar level was common in pregnant women, and the incidence of true diabetes mellitus was low. The glycosuria of pregnancy seems to be due to a lowering of the renal threshold and this usually is not associated with an elevated blood sugar. In about half of the pregnant women who showed no glycosuria following the ingestion of 50 grams of glucose, there was a lowering of the glucose tolerance curve. The Extton-Rose test was used in doubtful cases and consists in using two doses of glucose 30 minutes apart and examining blood and urine 30 minutes after the second dose.

Editorial

ANEMIA IN THE SOUTH

KARL SCHAFFLE, M.D.* of Asheville, North Carolina, recently made the striking statement that his associate, Max Riesenbergl, registered technologist, in examining the blood of several thousand persons over a period of 25 years, had discovered a hemoglobin average of 70 per cent and a red blood cell average count of between three and four million. He then asks why this should be so, particularly since most of these individuals ate well, felt fairly well and lost no time from work through illness. He reviews such diseases as malaria, tuberculosis, uncinariasis, pellagra and sprue which are common in the South, but these maladies do not explain the pretty general anemia to which he refers. It seems significant that even among his acquaintances he finds anemia in persons who are "good livers" and eat even four meals a day. He asks the question, "are our standards too high?"

Most of our hematological instruments were originally calibrated in Germany where before the war, Germans indulged in five meals a day in which sausage, liverwurst and other rich foods played a prominent part. This is in contrast to American eating habits where only one "square" meal a day is the rule. Throughout the South, surveys as recent as 1944 have indicated the frequency of diets too low in calories and it is well known that fried chicken, yams and grits, as well as corn bread, are common articles of diet and steaks and glandular organs are often difficult to obtain. Schaffle concludes that the anemia so common in the South points back to the red clay of the land whose productivity can scarcely be maintained by artificial fertilizers. Even the meat from animals grazing on such soil may fail to contain the quality of protein and minerals found in Northern animals.

The notable increase in grazing herds during the past six years throughout the South, especially in

* Schaffle, K.: Anemia in the South. South. Med. and Surg., May 1948, V. 110, No. 5, 138-140.

Florida, may exert a beneficial influence eventually both directly, and indirectly through the soil, on southern foods, but there remains the ancient problem in agronomy of how to render the soil adequate. It is possible that further diet analyses in the South might reveal not only a mineral lack but a lack of protein of good biological value. Until it becomes possible to produce sufficient animal protein, reliance might be

placed on vegetable protein, especially peanuts, which in Alabama alone is now a \$100,000,000 industry.

Schaffle's article is one more testament to the fact which is gradually emerging as possibly the most startling fact in medicine, viz., that the human race will not and indeed cannot, attain *perfect health* until the state of the soil and the state of agriculture have been adopted as primary medical problems.

Book Reviews

CONSTRUCTIVE MEAL PLANNING. By N. Philip Norman, M.D., pp. 72, Phototone Press, Inc., Passaic, N. J., \$2.50.

One of the authors of *TOMORROW'S FOOD** has written a book setting forth his ideas as to a specific method for planning meals.** A portion of this volume deals with the important fundamentals of diet and embraces food selection and food preparation and repeats the authors' well-known criticisms of certain phases of milling, preserving, and marketing of many edible food materials. He goes further and re-emphasizes the vital importance of a suitable soil upon which to grow nutritive-rich cereals, plants and animals.

Another portion of the volume, to which the greater attention is devoted in this instance by the author, deals with a conception of meal planning, which would avoid "mixed meals." A mixed meal, by definition, is one composed preponderantly of concentrated proteins, carbohydrates and fats served together in sizable quantities. The author recognizes that almost any natural food contains protein, fat and carbohydrate and that, for this reason, every natural food is, in a sense, a mixed meal. Critics of Norman's theory contend that the combination of protein, carbohydrate and fat in milk disproves his theory. But milk, says Norman, while it does contain protein, carbohydrate and fat, *does not contain these food elements in concentrated amounts*. Meals in which sizable portions of a concentrated protein food (steaks, chops, roasts, fish, seafood, etc.) are eaten in combination with large portions of concentrated starches, sugars and fats, have a vastly higher percentage content of the ternary elements than milk. Norman states that one would have to consume several quarts of milk to even approximate the ternary element content of a meal composed of a protein-rich soup, an average sized steak, ice cream, and other foods containing eggs or egg powder. It is his belief that a mixed meal is not comfortably or efficiently digested because of several considerations. Starch stimulates saliva but saliva has nothing to do with protein digestion. Protein, when

eaten, qualifies the amount and character of the gastric juice, and so does starch. For proper protein digestion, large amounts of hydrochloric acid and small amounts of pepsin are needed. The converse is true for starch digestion — it requires much pepsin and a small amount of hydrochloric acid. It is a well known physiologic fact that a concentrated fat partaken immediately before, during, or after a protein meal, will inhibit the response of the stomach and intestinal glands to the normal stimulus evoked by proteins and that this inhibitory action lasts from one to three hours. It is for this reason that fried foods have earned their reputation as "indigestants." There is no doubt in the reviewer's mind that this is good physiology (see Pavlov, *THE WORK OF THE DIGESTIVE GLANDS*, pp. 33-50) as it is well known that the rate of flow, the quality and the quantity of gastric and duodenal secretions are to a great extent conditioned by the stimuli of eating different foods and mixtures of foods. As a nutritionist Norman knows that clinical and subclinical manifestations of improper nutrition are widespread. He states that what are now popularly called malnutritional states are the result of excesses and deficiencies of the average dietary. He contends that there is a small chance of limiting the consumption of ternary excesses and increasing the consumption of accessory food factor deficiencies when meals are planned in accordance with the so-called mixed meal idea. Norman's plan, while strictly disciplinarian, allows a wide range and choice of foods of quality, and therefore cannot be criticized on a purely nutritional basis, no matter what one may think of his unusual planning of individual meals.

Norman is a medical revolutionist who thus far has never taken a position not supported by facts and for that reason his book deserves attention. In his opinion, breakfast should be the milk and fruit meal (includes berries, melons etc.); lunch the starch, salad, vegetable and fat meal; and dinner the protein, salad, vegetable and fruit meal, thus affording a *mixed diet* but not *mixed meals*. The reviewer is unable to pass any valuable critical judgment upon these conceptions largely because he does not know of any clinical experiments in which "pure" meals have been used. A reading of this phase of the book would seem to invite properly planned experiments in hospital wards or other institutions, with suitable controls. Pavlov has long ago answered the animal

* Rorty, James and Norman, N. Philip; *TOMORROW'S FOOD*, New York, Prentice-Hall, 1947.

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experimental question in the affirmative. Norman informs me in a personal communication he has attempted to competitively compare the results of his method of meal planning with the dietitians' balanced meal and with the average institutional dietary. The nearest that he came to effectuating this plan he states was several years ago when a sponsor was willing to underwrite such a project over a five year period. The institutional board of directors were enthusiastic but when the plan was submitted to the local Academy of Medicine it was vetoed by the doctors in control.

Inasmuch as Norman deletes practically all processed foods from his dietary, it may be regarded as quite iconoclastic and challenging to many elements in our present-day food industry and we would not be willing to approve of so bold a teaching unless we can find clinical evidence of its distinct superiority. We admit that nutrition has been rendered a vexingly complex problem by what we call *civilization* but can it be truly simplified by Norman's teaching? This, it appears to the reviewer, is the essential question which his book brings up.

The general conclusion, with which we find ourselves in agreement, is that the nearer we come to eating a whole cereal, fresh fruit, fresh vegetable, fresh milk, natural fat and fresh meat diet especially where these products spring from a rich, live replenished top-soil, the sooner we shall be able to learn the ultimate benefits to be derived from food.

Norman's book is provocative, and ought to be studied by all physicians and nutritionists, and he should be given a chance to prove in an institution what he claims to have been able to do in a considerable private practice over a period of more than 24 years. It is refreshing to read a book which on first impression seems faddistic but if one will take the time to read and re-read it one finds it filled with common sense facts without exaggerated claims or misleading statements which characterize books written by faddists. It is a thought-provoking-thesis which merits unprejudiced investigation. If it is factual and if it works, then it

should be approved and adopted by hospitals, institutions and the public. If it is fiction, then it should be labeled as such.

PRACTICE OF ALLERGY. By Warren T. Vaughan, M.D. and J. Harvey Black, M. D., Second Edition, pp. 1132, (\$15.00). C. V. Mosby, Co., St. Louis, Mo., 1948.

It is some years since *Practice of Allergy* has been available. After Dr. Vaughan's death, the work was revised and enlarged and brought up to date by the inclusion of new material by Dr. Black of Dallas, Texas. No work on general allergy could be more complete or practical. As might be expected, controversial problems are dealt with but lightly and there is an absence of any attempt to read allergy into pathological processes which obviously have nothing to do with allergy. Considerable space is devoted to the diagnosis and treatment of food allergy and this section appears to the reviewer to be adequate, painstaking and extremely valuable. No phase of this vast subject has been omitted. The book is highly recommended.

THE MECHANISM OF ABDOMINAL PAIN. By V. J. Kinsella, M.B., F.R.C.S. (Eng.) etc., pp. 230, (32 shillings, 6 pence), Australasian Medical Publishing Co., Ltd., Sydney, 1948.

This is a satisfactory treatise on abdominal pain and adequately reviews the history of the subject as well as embodying the author's own original observations over a number of years. Kinsella falls in line with recent American investigators who do not divorce tenderness from pain. Sir James Mackenzie did not believe a viscus capable of tenderness but Kinsella, like Palmer, has elicited tenderness in inflamed organs (ulcer, appendix) by palpation at laparotomy, the patient being conscious. In other words, a peptic ulcer is "sore." The dermal pain reflex may, however, result from what Mackenzie called a zone of irritation in the spinal cord. The book is clearly written and should prove useful to all clinicians.

General Abstracts Of Current Literature

ABSTRACT EDITOR — M. H. F. FRIEDMAN

Jefferson Medical College

1025 Walnut Street

Philadelphia, Pennsylvania

CLINICAL MEDICINE

MOUTH AND ESOPHAGUS

ASGIS, A. J.: *Applied nutrition for practicing dentists.* (Dental Items of Interest, January 1948).

Dr. Agsis was responsible for the collaboration of

James Rorty and N. Philip Norman, M.D. in their popular book, *Tomorrow's Food*, recently reviewed in this Journal. The author reviews the book briefly especially from the angle of dentistry and oral health as related to nutrition. The well-known work of Price, in this connection, is referred to also. One of the possibly significant statements in the book is quoted — "It is important to note that the best primitive diets



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STOMACH

LAKE, N. C.: *The aftermath of gastrectomy.* (Brit. Med. Jour., Feb. 14, 1948, 285-288).

Gastrectomy is considered to be the most permanently satisfactory method of dealing with peptic ulcer. The author discusses the "dumping" syndrome and other complications and describes two which have not previously been noted — omental necrosis and morning nausea. The latter is attributed to bile entering the stomach through the comparatively large orifice at night. The symptom is dispelled by sitting upright and taking breakfast.

HARTMAN, A. W.: *The problem of early diagnosis of cancer of the stomach.* (Texas State J. Med., Feb. 1948, V. XLIII, No. 10, 637-640).

Of the newer methods being used, the cytologic study of gastric secretions, as outlined by George N. Papanicolaou offers the greatest possibility as a cheap and accurate means of detecting the lesion in question. Cancer of the stomach is a silent disease in its early curable stages.

BOURNE, W. A., AND WOOD, W. R. F.: *Giant hypertrophic gastritis.* (Proc. Roy. Soc. Med., Jan. 1948, V. XLII, No. 1, 42-43).

A man 27 years old showed progressive loss of weight, vague dyspeptic symptoms, increasing dyspnea and severe anemia. The barium meal revealed multiple filling defects along the whole greater curvature and gastroscopy showed large nodular protuberances covered by reddened mucosa. After transfusions, a total gastrectomy was performed. The pre-operative diagnosis had been probable diffuse neoplasm. However, the specimen showed the characteristic appearance of "cerebral convolutions" and the pathologic diagnosis was giant hypertrophic gastritis. The patient's condition five months after operation was excellent.

LOWMAN, ROBERT M., SHAPIRO, ROBERT AND KUSHLAND, S. D.: *Extramucosal tumors simulated by gastric carcinoma.* (Am. J. Roentgen. and Rad. Th. 57, 6, 726. June 1947).

In the presented cases an adenocarcinoma of varying histopathologic structure was proved to have invaded the gastric wall producing an endogastric mass which simulated an extramucosal tumor. Clinically, the outstanding findings associated with these lesions

were 1) an upper abdominal mass, 2) epigastric pain, 3) gastrointestinal hemorrhage associated with anemia. The occurrence of an extensive colloid adenocarcinoma in a female, aged twenty-nine, is itself unique. The weight loss in each was moderate and none of the patients considered it of consequence. None of the clinical features or laboratory findings was of value in the main problem confronting the observer of determining whether the mass was benign or malignant.

These carcinomas fulfill all the roentgenological criteria for the diagnosis of extramucosal tumors. While it is reasonable to suspect a tumor of extramucosal origin when a sharply defined, rounded filling defect is noted, the diagnosis in such cases is based on probability only. The frequency of sarcoma as compared with carcinoma of the stomach is said to be only 1:100. However, adenocarcinoma producing roentgen defects as described are also infrequent. On the mucosal relief films, a coarse irregular reticular pattern was noted. The barium overlying the well defined endogastric tumor masses was arranged in an irregular polyhedral network. In many ways it was similar to the pattern produced by a slightly moistened sponge upon a dry blotter. In one case, marked diffuse destructive infiltration of the tumor into the mucosa could be demonstrated. In many places the mucosa was entirely replaced by the well differentiated tumor cells. Normal orientation of the cells especially in the submucosal area was lost. In another case the mucosa was infiltrated by the tumor and other areas of the overlying hyperplastic mucosa showed areas of destruction and ulceration. In a third case hypertrophic gastritis was combined with infiltration of tumor cells. The reticular pattern was therefore produced by the irregular nodulation and mucosal elevations projecting into the lumen.

FRANZ J. LUST.

BOWEL

RAVEN, R. W.: *Cancer of the rectum.* (Postgrad. Med. J., V. 23, p. 17, Jan. 1947).

Cancer of the rectum was responsible for the deaths in 1942 in England of 2,442 females and 3,698 males. Peak death rates were at the age of 65 for both sexes. Grossly the tumors may be classified as ulcerative, stenotic, polypoidal, or complex, while microscopically they are either of the columnar cell or mucoid cell type. Extension of the cancer is either direct or by way of the lymphatic or venous systems. Change in bowel habit, pain, and bloody discharge are the chief symptoms. The only chance for cure is radical excision. Preoperative preparation of the patient with cleansing of the field by means of sulfonamides is important.

JACKMAN, R. J.: *Submucosal nodules of the rectum: diagnostic significance.* (Proceed. Staff Meet. Mayo Clinic, V. 22, p. 502, Oct. 29, 1947).

A common finding on routine digital examination of the rectum are small submucosal nodules. These nodules are usually asymptomatic and are usually re-

garded by the clinician as being insignificant. However, the nodules may be malignant or may be potentially malignant.

The submucosal nodules examined microscopically in 87 consecutive patients were divided into four categories. Slightly more than half (49 cases) showed nodules which were the result of some injection treatment; these were classified as chemical tumors. Six patients had malignant nodules and eight patients had benign nodular tumors. Twenty-four had submucosal nodules which were considered inflammatory in origin.

Differentiation may be impossible without direct microscopic inspection. Since some of these nodules may be malignant and differential diagnosis is difficult without histologic study, it is recommended that these nodules always be excised for microscopic examination.

TAYLOR, S.: *Symptoms of Meckel's diverticulum*. (Lancet V. 253, p. 786, 1947).

Obscure abdominal symptoms may have their seat in a Meckel's diverticulum. If no other explanation for the symptoms can be found, Taylor recommends exploration of the last three feet of the ileum for anomalies.

Meckel's diverticulum is due to persistence of the vitelline duct which is usually obliterated at birth. The lumen of the duct may remain potent to give rise to a blind pouch of the intestine. Symptoms, usually acute, may vary but most nearly approach those of appendicitis. A Meckel's diverticulum is rarely diagnosed before operation.

Complications are varied and include intussusception, obstruction due to band or volvulus, ulceration with hemorrhage or perforation, neoplasm, strangulation and aberrant pancreatic or gastric gland tissue.

OLAUSSEN, A. T.: *Lesions in the small intestine causing melena*. (Nordisk Med., Jan. 28, 1948, 161-163).

Four patients were seen by the author in an 18 month period with melena resulting from lesions in the small bowel. Two of them suffered from Meckel's diverticulum with peptic ulcer, one had a simple ulcer of the ileum, and one had a neuroma in the small intestine. In diagnosis, the assumption of the presence of a bleeding peptic ulcer may cause serious delay. The presence of blood in the stools with non-hemorrhagic vomiting, and repeated occult bleeding in spite of negative X-ray findings in the stomach and duodenum ought to arouse suspicion of a small bowel lesion.

GIEDT, W. R.: *Public health aspects of diarrhea of the newborn*. (Northwest Med., Jan. 1948, V. 47, No. 1, 35-40).

Although problems associated with etiology, source of infection and mode of transmission of diarrhea of the newborn are in an unsettled state, we know the importance of isolation procedures in the control of

an outbreak and these procedures not only require ample space and sufficient trained hospital staff but sometimes the assistance of public health authorities whose function, frequently mandatory under state laws, are not always welcomed as they ought to be by the medical staffs of the hospitals.

CORBETT, R.S.: *Specimen of colon removed on account of severe pyoderma from a long-standing case of ulcerative colitis*. (Proc. Roy. Soc. Med., Dec. 1947, V. XI, No. 14, 871-872).

The cecum, and entire colon, along with three inches of the ileum were removed from a woman aged 46 who had suffered 12 years from chronic ulcerative colitis. The immediate indication for surgery was the presence of large superficial areas of ulceration on the thigh and calf of the right lower extremity, diagnosed as pyoderma. (Sometimes an erythema nodosum associated with this disease breaks down to the condition known as *pyoderma gangrenosum*). Another indication for the operation was a persistent mucopurulent rectal discharge. Previously a terminal ileostomy had brought about clinical improvement in abdominal pain and a rather severe anemia. The colectomy resulted in disappearance of the pyoderma and great improvement in general health. Pathologically the colon was thickened, contracted and imbedded in tough fibrous fatty tissue. Innumerable small polypi were found but no carcinoma.

LAGOZZINO, D. A.: *Epidemic infantile diarrhea*. (Northwest Med., Jan. 1948, V. 47, No. 1, 40-46).

Two epidemics of diarrhea in infants between one and eleven months of age are reported, and while an etiologic bacterial agent was not found, virologic studies are in progress. In three cases toxic encephalitis occurred. Chemotherapy and antibiotics merely controlled associated infection. Isolation and parenteral therapy were essential for recovery. Post mortem, the gastrointestinal tract was devoid of ulceration or inflammatory lesions.

PANCREAS

COLLINS, J. D.: *Acute pancreatitis*. (Northwest Med., Feb. 1948, V. 47, No. 2, 105-106).

The author divides cases of acute pancreatitis into (a) acute edematous pancreatitis (mild) and (2) hemorrhagic or necrotic (severe, fulminating). The etiology and pathogenesis are still far from clear. The onset of acute pancreatitis is sudden and associated with profound shock. The rise in the amylase content of the blood (Somogyi) is of help in diagnosis. Differentiation from perforated peptic ulcer and acute cholecystitis is not always easy. Conservative management is best, provided the diagnosis is clear — otherwise if laparotomy is done, cholecystostomy offers the best hope of help.

ANDERSON, H. A.: *Neoplasms of the pancreas.* (Northwest Med., Feb. 1948, V. 47, No. 2, 106-107).

Carcinoma of the pancreas should be suspected in a patient having a rapidly progressing syndrome of epigastric pain radiating to the back, weight loss with or without obstructive jaundice. Progressive jaundice, elevated serum lipase and normal amylase and fatty stools are essential features. Sometimes X-ray studies show pressure or traction on surrounding viscera.

LIVER AND GALLBLADDER

SWEDBERG, A. J.: *Surgical risk and after-effects in cholelithiasis.* (Nordisk Med., Jan. 23, 1948, 168-170).

A statistical study of over 1,000 cases of gallstone disease showed that a person having a first attack of gallstone colic has a 50 per cent chance of not having a second attack, without operation. He reports a 19 per cent operative mortality after the age of 50, while the mean mortality below 50 was only four per cent. The operation should be performed during a "quiet stage" and not while cholecystitis is active.

LONG, PERRIN H.: *Infectious hepatitis.* (Clin. Med., Feb. 1948, V. 55, No. 2, 35-37).

Infectious hepatitis or jaundice is the same disease as "catarrhal jaundice" a term which should no longer be used, in view of the knowledge gained in World War II, especially in the Mediterranean area. The commonest type is that in which an acute onset with jaundice proceeds to a clinical recovery in about six weeks. There is a mild type without jaundice and a third type which is protracted and chronic with remissions and relapses. Several methods are given for eliciting liver tenderness. In cases with jaundice the bromsulfalein test is valuable as a guide in treatment. The cause is a filtrable virus which resists the half hour heat of 550°C. Homologous serum jaundice is infectious hepatitis conferred by blood products or needles contaminated by the virus.

MACFADZEAN, R. AND STARR, K. W.: *Acute suppurative cholangitis with recovery on the use of penicillin and streptomycin.* (Med. J. Australia, April 10, 1948, V. 35, No. 15, p. 470).

A 38 year old truck-driver who had had previous attacks of biliary colic was admitted to hospital with colic, chills and fever and rapidly became irrational. He was tender and rigid in the right hypochondrium. At operation a single stone was found in the common duct and removed and about a pint of bile stained pus expressed from the duct by pressure on the engorged and discolored liver. Cholecystectomy and

choledochostomy were performed. Two million units of penicillin were used and a total of 20 grams of streptomycin. He made a rapid and perfect recovery. The recovery rate from suppurative cholangitis associated with multiple liver abscesses is low and it is thought that the use of streptomycin in this case (even though the infecting organism was not obtained) contributed greatly to the excellent result.

CAMERON, D. G. AND NEWHOUSE, M. L.: *Chronic hepatitis treated with methionine and choline.* (Brit. Med. J., Feb. 7, 1948, 253).

Six patients suffering from chronic hepatitis were treated on a high protein diet with a supplement of 15 grams of methionine daily for six weeks and choline chloride in the same dose for a further period of three months, but no change was noted in the clinical condition of the patients during this time, and the variations which occurred in the plasma proteins (slight fall in globulin, chiefly) did not seem to be due to the treatment.

SCOTT, K. B. AND TOVEY, G. H.: *Homologous serum jaundice.* (Brit. Med. J., Jan. 31, 1948, 196-197).

A case of hepatitis in a primipara is described, complicated by a breast abscess. The cause was a plasma transfusion given because of post-partum hemorrhage 79 days before the onset of the jaundice. The authors describe methods of tracking down and reported infected batches of plasma.

APLEY, J. AND WALLIS, H. R. E.: *Homologous serum jaundice in infancy.* (Brit. Med. J., Jan. 31, 1948, 197-198).

The authors report two fatal cases of hepatitis in infants. One developed jaundice 63 days after plasma transfusion and the other 122 days after infusion. Possibly homologous serum jaundice frequently goes unrecognized in infancy.

McPHERSON, W. G. AND HUGHES, C. R.: *Echinococcus cyst of the liver (report of four cases).* (Cleveland Clinic Quart., April 1948, V. 15, No. 2, 92-98).

Four cases of echinococcus cyst of the liver are reported and it is emphasized that pain referable to the upper right quadrant similar to that in gall bladder disease is the outstanding symptom. The liver in all four cases was enlarged but not functionally impaired. Eosinophilia is diagnostically important only in early cases. The skin test (cutaneous reaction of Casoni) is the most accurate diagnostic test, being positive in 90 per cent of cases. Surgical evacuation of the cysts at least partially relieved the symptoms in the cases followed.

GEEHAN, J. W.: *Diagnosis and treatment of stones in the common bile duct.* (North-west Med., March 1948, V. 47, No. 3, 195-197).

Twenty-five years ago few surgeons performed any operation on the biliary tract except cholecystostomy, but now cholecystectomy has replaced this operation and the common duct is frequently explored for stones and debris. It is generally recognized that 10 to 20 per cent of patients with gall stones have stones in the common duct or hepatic ducts. Jaundice renders exploration of the common duct imperative. Stones in the ducts are the most frequent cause of continuance or recurrence of symptoms after biliary surgery. Biliary dyskinesia may simulate a stone but can be quickly relieved by 1/200 grain of nitroglycerine under the tongue. A dilated duct always should be explored.

HJORTSJO, C. H.: *The internal topography of the liver studied by means of X-ray and injection technique.* (Nordisk Med., April 9, 1948, V. 38, No. 15, 745-748).

Corrosion preparations have been produced from the bileduct system and that of v. portae, in some cases also from the systems of the a. hepatica and the vv. hepaticae. The preparations have been orientated in a correct manner according to stereoscopic cholangiograms, performed with the organ in situ. The ramification formed by the v. portae is divided into one right and one left chief section by a main boundary fissure corresponding to the right sagittal fissure. An incidental fissure corresponding to the falciform ligament and the left sagittal fissure divides the left main part into a medial portion and a lateral one. Thus the lobus quadratus, and in most cases also the spigelian lobe without its processus caudatus, will belong to the medial portion. In the lateral portion, a dorso-lateral segment and a ventro-lateral one have been observed, and in the right main part a dorso-caudal segment, an intermediate segment and a ventro-cranial one. All these segments have displayed a rather characteristic architecture and have been separated from one another by fissures. In these fissures, and in the main boundary fissure and the incidental fissure too, runs the vv. hepaticae. In cross section the bileducts have an elliptic form. In most cases they fairly well follow the corresponding v. portae rami. The bileduct to the dorso-caudal segment has a rather original curved (sometimes angular) course, when "riding on" the right main branch of the v. portae. Certain projection conditions in the cholangiograms may originate in a not exactly sagittal position of the main boundary fissure. When an artery, a bileduct and a v. portae ramus cross one another simultaneously, the artery is always found lying between the bileduct and the v. portae ramus.

ULCER

KIRKETERP, A. P.: *Causative factors in hematemesis and melena.* (Nordisk Med., Jan. 23, 1948, 156-161).

Detailed histories were obtained on 25 patients with hematemesis and melena in order to determine aggravating causes. Twelve patients had suffered minor physical trauma and ten had been under emotional distress in the days or hours preceding the hemorrhage. One of the three patients whose hemorrhages were apparently spontaneous had multiple gastric ulcers which in 22 years had caused 25 major hemorrhages, his brother having died from a similar disease.

MUKHERJEE, S.: *On the chemistry of the antacids.* (J. Indian Med. Assoc., Oct. 1947, V. XVII, No. 1, 7-10).

It is often found that any single antacid fails to satisfy all the requirements of the patient, so combinations are advisable. Thus, a quick acting antacid is added to a slow acting one in order to give immediate relief. Similarly, an antacid having a laxative action may have to be added to another having astringent properties. It has been suggested that four c. c. of milk of magnesia with 200 c. c. of colloidal aluminum hydroxide prevents the undesirable rise of pH caused by milk of magnesia and the constipating effect of the hydroxide. Many such combinations are possible.

SZASZ, T. S.: *Psychiatric aspects of vagotomy — a preliminary report.* (Ann. Int. Med., Feb. 1948, V. 28, No. 2, 279-288).

Ulcer patients have a strong need to "receive." Following favorable results of vagotomy, the absence of symbolic oral gratification due to cessation of dietary and other medical measures is thought to be potentially harmful and it is suggested that the clinical results may be improved somewhat if the patients are permitted to continue with certain psychologically meaningful aspects of their preoperative medical regimens after vagotomy.

WINGREN, A. J. E.: *Perforating ulcer.* (Nordisk Med., Jan. 23, 1948, 163-166).

The author reviews a series of 130 patients treated for perforation by surgery. He found that gastrotomy was preferred because there were fewer post-operative complications than with other methods (suture, drainage, gastro-enterostomy). Among six patients re-treated surgically, peptic ulcers were found. Intensified post-operative care of a conservative nature is recommended.

RIESE, J. A.: *Peptic ulcer — is it a psychogenic disease?* (Rev. Gastroent., Feb. 1948, V. 15, No. 2, 159-161).

The author states that undoubtedly peptic ulcer is

a psychosomatic disease, but that psychogenic factors have been found most prevalent as a cause for recurrence, and to a lesser degree as the primary cause of peptic ulcer. (He perhaps partially disqualifies himself as a judge by admitting that he is not a psychiatrist).

VERDOORT, F. AND PARMENTIER, CH.: *The Wohlgemuth reaction in gastro-duodenal ulcers.* (Acta G. E. Belgica, Jan. 1948, V. XI. No. 1, 49-53).

While many gastroenterologists have abandoned the Wohlgemuth reaction because of diverse views concerning its interpretation and while it has not the positiveness of a Widal or Wassermann reaction, the author believes it has a definite value in detecting associated pancreatitis and in explaining the cause of death in certain operated cases of ulcer who develop a rapid pulse and die within 10 days following operation, with no explanation for the death except pancreatic irritation. Using the test he has been able to trim down his mortality rate following operation by diet, insulin and atropine, a regimen which reduces the positivity of the Wohlgemuth reaction as well. The test aids in the selection of cases to be subjected to operation.

BURNEN, V. G.: *Surgery of peptic ulcer in prison.* (Rev. Gastroent., March 1948, V. 15, No. 3, 208-217).

The incidence of peptic ulcer in prison inmates is low, which casts doubt upon the validity of current teaching with respect to the influence of mental factors (worry, anxiety and other emotions) on the production of ulcer. Since these patients, following operation, do well on the rough prison diet, doubt is also cast upon our conceptions of the advantages of special diets. The author favors gastroenterostomy in duodenal ulcer.

SURGERY

GILCHRIST, R. K. AND DAVID, V. C.: *Radical excision of cancer of the colon.* (Ann. Surg., V. 126, p. 421, 1947).

In cancer of the colon the spread is usually checked at lymph nodes. Spread may occur from node to node by collateral vessels but is usually limited. The best surgical results are obtained when the resection is wide and includes the growth and also as much of the lymph tissue of the area as possible.

The authors present the results of resection of colonic cancer in 200 patients. Five to ten year cures were obtained in 78.5 per cent of the cases where the lymph nodes were not involved. With lymph node involvement the five year survival was 37.5 per cent when there was extraperitoneal extension; 61.5 per cent in cancer of the right colon; and 51.4 per cent in

cancer of the sigmoid or intraperitoneal part of the rectum. Where there was extraperitoneal involvement of the colon the prognosis was as good as for cancer of various regions of the colon.

The post operative mortality rate may be expected to be reduced with wider adoption of chemotherapy. Pregnancy complicated by cancer of the rectum was met with in three cases and two patients survived longer than five years. The authors emphasize that repeated examinations should be made for possible new cancer growths in patients already operated for colonic cancer.

HENDRY, W. G.: *Superior mesenteric arterial occlusion: recovery without resection.* (Brit. Med. J., Jan. 24, 1948, 144-146).

A pre-operative diagnosis of superior mesenteric arterial occlusion was made in a man of 64 suffering from profound shock (B. P. 70/50, pulse 120, temp. 95° F.) and abdominal pain, and confirmed by laparotomy. Since the involved segment of gut appeared viable, resection was not done because of the condition of shock. He made a recovery by means of suction, saline and blood transfusions and heparin intravenously. Diagnostic features are profound shock, partial intestinal obstruction and peritoneal irritation evidenced by rebound tenderness. To be differentiated are — coronary thrombosis, acute pancreatitis (which is not associated with progressive vomiting) and long-loop strangulation. The shock was due to the escape of a large quantity of plasma by transudation as three pints of spontaneously coagulable fluid were evacuated from the abdomen.

EXPERIMENTAL MEDICINE

PHYSIOLOGY

AUGUR, V., ROLLMAN, H. S. AND DEUEL, H. J.: *The effect of crude lecithin on the coefficient of digestibility and rate of absorption of fat.* (J. Nutrit., V. 33, p. 177, Feb. 1947).

Large doses of cottonseed oil or hydrogenated cottonseed oil when fed to the rat resulted in diarrhea. Addition of crude lecithin preparation to the diet at about 20 per cent levels decreased the diarrhea. The phosphatid addition also increased the rate of fat absorbed from the intestine.

LANDBOE-CHRISTENSEN, E. AND BOHN, C. L. S.: *The curative effect of pure duodenal secretion from swine in cases of pernicious anemia.* (Acta Med. Scand., V. 127, p. 116, Jan. 1947).

Duodenal loops with fistulas were prepared in pigs. From these was collected an alkaline, slightly opalescent, viscous secretion. This secretion was given

orally to patients with pernicious anemia who were being maintained on a non-vegetarian diet. In one elderly patient the response was not striking but in a younger subject the response was definite. Megaloblastic bone marrow was converted to normoblastic bone marrow and the reticulocyte count was increased.

BLOKHIN, N. N. AND LYZLOVA, S. N.: *Nervous regulation of carbohydrate absorption in the animal organism (dog.)*. (Bull. Exp. Biol. U. S. S. R., V. 22, p. 21, 1946).

The London technique of angiostomy was used in dogs. Calcium gluconate or potassium phosphate was introduced into the subarachnoid space. The potassium phosphate was found to increase greatly the absorption of glucose introduced into the gastrointestinal tract, as determined by the glucose content of the portal venous blood and the femoral arterial blood. A maximum of 93 per cent difference between the arterial and venous blood glucose content was obtained in one-half hour following the potassium injection. In control experiments the maximum levels of blood glucose was reached only after the first hour. Calcium gluconate tended to inhibit the absorption of glucose and decrease the arterial-venous differences in blood glucose content. These results were correlated with the fact that potassium acts on the sympathetic centers while calcium acts on the parasympathetic centers.

METABOLISM

SHEEHAN, H. L., SPENCE, A. W., FRASER, R., SIMPSON, S. L. AND ARMSTRONG, C. N.: *Discussion of Simmond's disease*. (Proc. Roy. Soc. Med., April 1948. V. XLI, No. 4, 187-195).

The common idea that persons with Addison's disease are emaciated is not true, since actual weight figures indicate that nutrition is fairly well maintained except immediately before death. If one-quarter to one-third of the anterior pituitary escapes destruction the syndrome does not develop. There must be *long-standing and severe destruction* to produce the disease. Possibly the term "Simmond's Disease" should be applied only to those cases exhibiting manifestations of panhypopituitarism brought about by organic lesion, and not to those milder cases in which for instance, the only feature of hypopituitarism

is a disturbance of gonadal function. It would be more satisfactory to refer to Simmond's Disease and to the incomplete forms of the syndrome in terms of their pathology — post-partum necrosis, tumor, syphilis, etc. The disease *par excellence* which is confused with Simmond's disease is anorexia nervosa. The intravenous insulin tolerance test, a urinary steroid assay and tests of thyroid function are valuable in diagnosis. In treatment, thyroid extract is needed in doses sufficient to raise a low B. M. R. and depress the blood cholesterol to normal. Desoxycortone may be employed where adrenal insufficiency is present as indicated by the Kepler test. Testosterone is undoubtedly of value. The hypoglycemia may be combated by Upjohn's lipid extract of the adrenal cortex.

MISCELLANEOUS

LEDERER, J.: *Influence of the acidity of the gastric juice on the diffusibility of iron*. (Arch. Internat. Pharmac. Therap., V. 75, p. 436, Jan. 1948).

Trivalent iron mixed with neutralized gastric juice is not dialyzable. It becomes dialyzable when the gastric juice is acidified to pH below 3.5. Bivalent iron mixed with neutralized gastric juice is dialyzable but its diffusibility increases with acidification. The maximum diffusibility is at pH 3.5. These differences of the diffusibility of the forms of iron explain the better absorption of the ferrous form.

FAIRWEATHER, D. S. AND O'SULLIVAN, H. J. L.: *Gastric dilatation, megacolon, and idiocy in identical twins*. (Arch. Dis. Child., V. 22, p. 236, Dec. 1947).

The chief interest in this report is the association of atonic dilatation of the stomach, Hirschsprung's disease, the coeliac syndrome, and idiocy in identical female twins. Two siblings, one born before and the other after the twins, were normal. The onset of megacolon symptoms followed an attack of gastroenteritis at the age of five months so that apparently the genetic factors may have depended on environmental factors to some extent. There was considerable general emaciation with abdominal distention in both children, frequent fatty stools, and stunted growth. The stomach was found to be dilated to the extent of displacing the heart upwards. Radiologically the twins showed redundancy of the colon as well as megacolon.

Pathogenesis of Hepato-Jaundice and its Surgical Approach

By

B. O. PRIBRAM, M.D., PH.D., F.I.C.S.

NEW YORK, N. Y.

SURGERY IN HEPATO-JAUNDICE seems to be somewhat paradoxical as many authors use the term medical jaundice synonymously, meaning that this disease is out of bounds and a forbidden area for the surgeon. Personally, I have never been satisfied with such a strict distinction and I hope to show that medical jaundice indeed might become a surgical jaundice, while, on the other hand, I feel that surgical jaundice should never cease to be a medical jaundice as well.

PATHOGENESIS OF HEPATO-JAUNDICE

In spite of the great advance that has been made in the knowledge of hepatitis, the way in which jaundice develops is still not quite clearly understood. Among the great majority of physicians of the 18th and 19th centuries, the "dyscrasic" theory of jaundice still prevailed. According to this theory, a wrong mixture of the human liquids — one of them being the bile — was considered the main cause of most internal diseases. Jaundice was consequently connected with a *hyper-activity* of the liver and over-production of bile which prevailed in the blood-bile mixture. Only a few authors (Selley and Stoll, J. P. Frank, Breschet), not satisfied with the rather vague "dyscrasic theory," and impressed with the gastro-duodenal symptoms, regarded "bilious fever" as a "degeneration of a gastro-enteric catarrh" and jaundice itself as being caused by upward-spreading inflammation. However, Littré pointed out that the frequency with which jaundice is met in these fevers proves that implication of the liver cannot be regarded as a mere complication of a gastro-duodenal catarrh, but that it is more likely that the latter and the liver disease have a more intimate connection and have a *common cause*. Similar conceptions were voiced by Stokes and Graves at the beginning of the 19th century.

The humoral theory of jaundice received some support from the discovery of the direct transformation of blood into bile, the first instance of which was described by Virchow, who found that in old hematoma, hemoglobin was transformed into hematin, a substance very similar to bilirubin. This discovery brought the first conclusive evidence of an extra-hepatic origin of bile pigment. Experiments in this direction were further carried out by Zencker, Valentin and Jaffe. Supporters of the "dyscrasic" conceptions believed in a non-hepatic "black degeneration of blood into bile" (Breschet — 1821). Other physicians, however, believed in an obstructive cause for all cases of jaundice. How far these mechanical conceptions were carried can be seen by the fact that many old clinicians of the 18th and 19th centuries believed that hepatic jaundice might also be caused

by fecal masses accumulating in the right colon during constipation (Frerich's).

Virchow, formerly a supporter of the hematogenous theory of jaundice, entirely changed his mind after the impressive observation of a severe inflammation of the duodenum in a case of catarrhal jaundice. He found an edematous swelling of the mucous membrane around the papilla and a whitish plug consisting of epithelial masses and mucus, blocking the papilla of the common duct. Based on these findings, he formulated his mechanical theory of the pathogenesis of catarrhal jaundice and extended this even to the origin of jaundice in pneumonia, typhoid and phosphorus poisoning.

Having had the opportunity to operate on quite a few cases of so-called catarrhal jaundice, could observe in several instances, these whitish plugs of mucus and epithelial debris supposed to be the cause of an obstruction of the common duct. However, these findings appear in another light through the following observations. When opening the common bile duct, there was never an increased pressure as is the case of mechanical obstruction. The bile was frequently discolored and transformed or rather replaced by a whitish turbid liquid. Whitish plugs, as described by Virchow, were found lying loosely in the ampulla. They were found also in some cases in the gallbladder.

These findings strongly suggest that this plug of mucous and epithelial debris originates in the bile-duct system and the gallbladder and is due to sedimentation of the whitish turbid liquid. The collection of this mucous and epithelial debris above the papilla is related to the absence of bile, which normally cleans the whole bile duct system by permanent drainage. It is a *symptom* of a primary *acholia*, but not the *cause* of jaundice in a mechanical sense.

Virchow's theory is now abandoned by most pathologists. However, the idea that obstructive causes, either of extra-hepatic or intra-hepatic nature, might play an etiological role, is still seen in several conceptions. Pavel and his co-workers believe in the etiological importance of a spasm of the sphincter of Oddi. Mayo-Robson, in 1900, maintained that swelling of *pancreatic tissue*, which often encircles the ampullar part of the common duct might cause a mechanical obstruction through compression.

Theories about an *intra-hepatic obstruction* of the bile ducts go back to the 19th century as well. As

far back as 1895, Hanot spoke of an intra-lobular obstructive jaundice, without, however, giving convincing facts. Hoppe-Seyler maintained that the obstacle must lie at the level of the bile capillaries. He believed that, especially in the atrophic stage of acute yellow atrophy, the intra-lobular bile ducts may be partially blocked through necrotic epithelial debris or kinked and collapsed through disorganization of the structures of the liver lobules — a theory which was further developed by Eppinger based on an extensive study of microscopic pictures.

Many observers, not satisfied with the findings around the papilla and the common duct, and, especially, pointing out the absence of any dilatation of the common duct above the assumed obstruction, think that when there is an obstruction, the obstacle must be higher up. Dilatation of the bile capillaries, which might give a good hint about the location of the obstacle, is found at the periphery of the acini. Here we can observe cracks in the walls similar to those seen in obstructive jaundice. The larger bile ducts, on the other hand, bordering the portal vein branches, are narrow or at least not dilated. The common duct also has a rather narrow lumen and definitely shows no signs of dilatation. The conclusion, therefore, drawn by Aschoff et al, was that the ampulla, the Hering canal, is the site of injury and block.

When the wall of the ampulla is torn, communication between the liver cells and the capillary bile ducts is interrupted. Inflammatory effusion and cellular infiltration in this case might interfere with the normal outflow of bile into the bile ducts and, on the other hand, open the communication with the lymph spaces.

The following photograph gives an impressive illustration of bile just pouring out through the torn wall of a small bile duct.

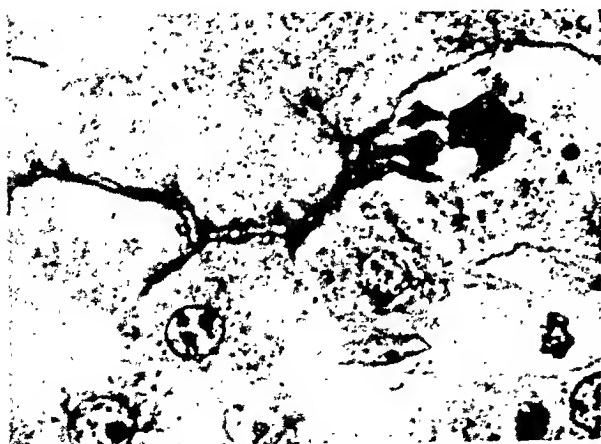


Fig. — 1. Rupture of intracellular bile capillary with extravasation of bile. Taken from P. Klemperer, et al. Arch. Path. 2:631-652, 1926.

In many cases of hepatic jaundice clots and thrombi are observed in the small bile ducts which "plug the bile capillaries like a cork" (Affassanief), furthering

tearing of the walls and liver cells. Eppinger has studied these bile thrombi with a special staining method. He considers that the bile thrombi are frequently the real cause of jaundice in a mechanical sense.

However, there are many objections against this intra-hepatic mechanical theory of jaundice as well. Hyieda, for instance, observed that in experimental poisoning with toluidine dilatation of the bile capillaries and the appearance of bile thrombi does not parallel the appearance of jaundice at all. The latter sometimes precedes the former. The observations of Clara prove that dilatation of the bile capillaries is not caused by stasis. He observed that such dilatation occurred after the injection of decholin and without jaundice. Moreover, the number of these bile thrombi found in the capillaries is sometimes very small and is by no means related to the severity of the jaundice. The network of the capillaries is, on the other hand, so widespread, that it leaves ample opportunity for the bile to find another way through communicating bile ducts if there is a local obstruction.

The liver is actually in a position to deal with much greater than normal amounts of bile in case of necessity, as Rich recently pointed out. One hepatic duct may be entirely obstructed by new growth and nevertheless, jaundice may be entirely absent as the other liver lobe may take up all the bile drainage without marked signs of obstruction and regurgitation jaundice. Experiments carried out by P. MacMaster and Rous proved that three-quarters of all bile ducts could be ligated without the appearance of jaundice. This again shows the improbability of a purely mechanical explanation of jaundice by an assumed intra-capillary obstruction found here and there. There is further the fact that when jaundice starts, whatever its intensity might be, bile thrombi are often rare and their number *increases* with the duration of jaundice. This definitely points against the etiological significance of the bile thrombi, but suggests rather a secondary deposition. It is helpful and enlightening to compare jaundice in hepatitis with the retention of products of metabolism in the blood in nephritis. We can easily compare the bile thrombi to the casts in the tubuli of the kidney. These casts are *symptoms* of an inflammatory process, and they are certainly not the cause of incomplete diuresis or azotemia in a mechanical sense. The same probably holds true for bile casts. They are primarily inflammatory effusions and secondarily bile stained. *This is one symptom of the inflammatory process involving the whole liver but not the mechanical cause of jaundice.*

Dilatation of the bile capillaries is not a proof of a peripheral obstruction as mentioned already. Such a local dilatation can be observed quite independently and is probably related to the *excretory* function of the liver cells and the *cholokinetic* activity of the capillaries. This point will be discussed later.

Jaundice almost regularly develops in cases of

cholangitis. However, this is only a complication in some cases of hepatitis and accounts in no way for the development of jaundice in hepatitis in general.

The concept that jaundice in hepatitis is caused by *disruption of the liver cell cords and cell destruction* is now accepted by most authors. However, there are strong objections also against this theory.

(1) In Weil's disease, jaundice can be very pronounced and at post mortem and in biopsy specimen hardly any disruption of the liver cell cords or a cell necrosis can be seen.

(2) There are quite a few cases of yellow atrophy observed with widespread destruction of the liver lobules while no jaundice at all is observed clinically.

There is ample clinical evidence that the function of the liver in producing hepatobilirubin goes on even in cases of very serious cell damage. In acute atrophy of the liver, one is indeed surprised to see that sometimes in the last stages of the disease when the patient is already in a state of hepatic coma, jaundice diminishes. This has been explained by the assumption that the function of the liver cell in producing bile has stopped altogether. This is wrong. The diminishing of jaundice parallels the temporary draining of bile into the duodenum. One sometimes finds at post mortem fairly well-bile-stained feces in some parts of the bowels, while other parts contain completely acholic feces (Jones and Minot, Lucke, own observations). The bile-producing function of the liver cell goes on till the last.

Here indeed does surgery come into the picture, both in contributing observations that may help to explain the pathogenesis of jaundice, and in showing new ways of treatment. In the last fifteen years, I have operated on several cases of chronic icteric hepatitis for various reasons. Some of the cases were dragging on in a painless jaundice with complete absence of bile in the duodenum, suggesting a malignant obstruction. Other cases would not improve under medical treatment and would show a definite tendency to develop into acute atrophy of the liver.

The operative findings in these cases were quite remarkable. The aspect of the liver was varying in degree of damage. The common duct was of normal size and the majority contained no bile at all. It was filled instead with a whitish turbid liquid. The gallbladder was always enlarged and contained either dark-green inspissated bile or the same whitish turbid liquid. On slight pressure, the gallbladder could be easily be emptied. The papilla was found patent in all cases.

Striking observations could be made when examining the duodenum. In three out of twelve cases, duodenal ulcers were found quite unexpectedly; they did not cause any clinical symptoms. In one case a free perforation was observed, also without having caused any clinical symptoms.

CASE REPORT

A man 48, a doctor, had always been in a good state of health with the exception of an attack of malaria 27 years ago.

On March 2, 1945, after a rich, fatty meal, he had the sensation of having eaten too much and of being very full. He took some purgatives, but the ill-feeling did not subside. Two days later, painless jaundice developed, which dragged on for several weeks. The liver was enlarged, soft and never tender. Appetite returned soon. Jaundice was persistent for seven weeks, when he was admitted for surgery.

Laboratory Findings:

4/23/45

Blood: 2.5 mill. red cells. Moderate central depression. Anisocytosis, slight polychromasia.

Number of White cells	13,500
Multilobed	75.0%
Band Forms	3.0%
Lymphocytes	18.0%
Large Mononuclears	4.0%

Number of blood platelets increased.

Sed. Rate (Westergren): 110 mm. after 1 hour
137 mm. after 2 hours

Stool: (4/24/45)

Color	Tarry
Consistency	Pasty
Hydrobilirubin	Slightly positive
Reaction	Alkaline
Mucus	Small amount
Insufficiently digested muscle fibers in excess.	
Fats not elevated.	

Blood: very strongly positive.

Swinging temperature set in with frequent rigors. However, the general state of the patient remained fairly good. No complaints. No pain whatsoever in the abdomen.

Repeated stool examinations revealed large amount of blood and urobilin, but, in other specimens, urobilin was not present at all. On introducing the duodenal tube, the bottom did not pass through the pylorus but some fresh blood came out occasionally. The gastric juice was acid. A plain X-ray picture revealed an enlarged gallbladder but without any stones. The diagnosis was still not quite clear.

DISCUSSION

The onset of the disease was doubtless that of an acute infectious hepatitis of the catarrhal jaundice type following food poisoning*. However, the picture changed somewhat, when, four weeks after the onset, swinging temperature appeared, suggesting development of an acute cholangitis as a complication. Quite confusing was the considerable hemorrhage into the intestine which, according to the results of the duodenal tube, could probably be located in the duodenum. The seriousness of the hemorrhage, which was more of a chronic character, caused the red cells to drop from four to two millions. Vitamin K was of no effect.

Since the jaundice, on the other hand, assumed more and more an obstructive character, the diagnosis of a bleeding carcinoma at the papilla was considered. However, the consistency of the liver remained soft and its edematous character could be proved by the fact that after intravenous injection of 20 cm. of a 50% glucose solution the size of the liver decreased almost immediately to remarkable degree. Obstructive Jaundice could therefore

* See Pribram Am. J. Digest Dis. June 1946.

be excluded. Hemorrhage eventually was stopped by injection of Neo-hemoplastin. Operation was decided on and performed under spinal anesthesia.

OPERATION (May 7, 1945)

Costal incision: Fair amount of whitish fluid in the abdominal cavity. The liver was enlarged, edematous and of yellowish-brown color. The gallbladder was enlarged, but the wall did not show any signs of inflammation. The content was aspirated in situ, and a whitish fluid obtained, similar to that found in the abdominal cavity. The fluid was preserved for microscopic and bacteriologic examination. As the gall bladder and liver were lifted up, the same whitish liquid poured out of a hole in the anterior duodenal wall. It was a ruptured ulcer, free perforation without any adhesions around it.

The cystic duct was patent. Upon the slightest pressure on the gallbladder, the liquid pours out again through the ruptured duodenal ulcer, giving further evidence of complete patency of the papilla. The fingers of the left hand felt retro-duodenally around the head of the pancreas. This part of the pancreas was grossly enlarged and extremely hard. It gave the impression of multiple impacted stones. The pancreatic tissue surrounded and encircled firmly the lower part of the common duct and the papilla. The duct was, however, not distended and on opening the common duct, a sound of medium caliber easily could be passed through the papilla.

The complete absence of hydro-bilirubin in the feces which seemed to support the assumption of obstruction found a simple explanation in the complete acholia. The gallbladder was now opened and some whitish mucoid porridge-like stuff of epithelial debris was found in the same stuff which was found in the common duct and above the papilla, apparently the same kind of mucus plug as is often described. The ulcerated part of the duodenum was excised for histology and a cholecysto-duodenostomy was performed.

During the operation, yellowish-brown bile started draining down from the hepatic duct, a sign that suddenly excretory block in the liver had been abruptly released. The next morning, yellowish-brown bile drained profusely through the duodenal tube, introduced through the nose before the operation.

Uneventful and satisfactory recovery proceeded until the eighth day when the patient developed a rapidly progressing parotitis. He stated that for months he had had a discharge of pus from his right ear. The whole neck and face became edematous. The temperature rose to 102 degrees.

The pulse became irregular, necessitating digitalization. Sulfonamide injections were given for two days, but then, in consideration of the damaged liver, it was given up in favor of penicillin. The temperature came down nicely and the parotitis was well-localized and showed signs of beginning fluctuation. The patient was in good condition. Blood transfusion is performed with 300 cc. (blood donor A, compatibility proved by cross matching). The whole amount was administered slowly in 30 minutes. An hour later, sudden violent rigors set in and the patient died within a few minutes.

Post Mortem: The color of the skin and the sclera were still slightly jaundiced.

Liver: The liver was very soft and friable and of brownish color — surface smooth, and shining. The anastomosis between the gallbladder and duodenum was well healed without any leakage. The cystic duct was opened on a probe down to the common duct, which contained some yellow-

ish-brown bile. The probe could be pushed towards the papilla and easily into the duodenum. The pancreatic tissue surrounded and encircled the papilla in the retro-duodenal part. The head of the pancreas was hard, but not of the stony consistency found at operation. The whole head was certainly much smaller than previously. Several cuts were made through the pancreas head which gave the impression of a sub-acute pancreatitis. Apart from a few yellow patches on the capsule, no signs of fat necrosis were found in the surrounding tissue. The mucus membrane of the duodenum was hyperemic but otherwise did not show any pathologic changes. The spleen was barely enlarged, but had a definite septic character. The pulp could be easily wiped away from the cut surface. The heart was in diastole and the heart muscle was very soft and friable. The mitral valves were thickened from an old inflammatory process.

Specimen of Duodenum: Histologic examination of the excised ulcerous part showed the epithelial lining to be missing in most of the section. The submucosa with Brunner's glands is intact everywhere. There was scarcely any inflammatory reaction in the tissue with the exception of one place, where an infiltration with round cells in the submucosa could be seen. This infiltration was present in the adjacent muscularis as well. No evidence of malignancy was seen.

Diagnosis: Simple duodenal ulcer.

Aspirated fluid from the gallbladder (specimen taken at operation).

Chemical examination: **Normal Variation:**

Diastase — 25 units	(25 to 50 units)
Lipase — 0.2 units	(0.2 to 2 units)

Sediments: Leucocytes, and epithelial debris, mucus, no bile pigments.

Bacteriologic Examination: Pure colonies of bac. lactis aerogenes mimosus, capsulatus in good growth.

Microscopic Liver Examination:

Acute hepatitis with marked infiltration around the small bile ducts (cholangitis). Disruption and disorganization of the liver cell cords in many areas. Fatty infiltration of moderate degree.

Pancreas: Sub-acute inflammation. Infiltration with round cells.

Summary:

In a man of 48 following "food poisoning" with a fatty meal, an acute icteric hepatitis developed, followed by a swelling of the head of the pancreas (acute edematous pancreatitis). A duodenal ulcer developed, probably on the basis of an acute duodenitis, with the signs of a trophic ulcer without causing any pain and which even perforated without causing any pain or other clinical symptoms. Secondly (after four weeks duration) a cholangitis, most likely by ascending way, developed as a complication. Bacteriologically bacillus lactis aerogenes capsulatus in pure culture was found in the gallbladder and bile ducts. The question as to the pathogenicity of this bacillus has to be left open. The possibility that it was the cause of the cholangitis cannot be discarded.

Two striking observations have to be registered: (1) The ulcer on the anterior wall of the duodenum developed without causing any pain. Even when perforating, not the slightest feeling of discomfort was

felt by the patient, who, being himself a Doctor, certainly has observed all the symptoms of his disease very carefully. The perforation took place apparently the day before the operation was performed. (2) The second striking observation was the sudden onset of excretion of normal bile while manipulating on the external bile ducts. This is the more remarkable as all the findings, the complete absence of any bile in the biliary duct system, and the replacement by turbid, whitish liquid with abundant secondary sedimentation, indicated the long period of complete excretory block of bile-excretion. No special surgical credit could be claimed for this lucky event in the sense of removing an obstacle.

Sudden onset of bile-secretion following operation was similar in all cases. In some of them bile secretion started either directly on the operating table, or, it started on the same or following day. This brought a dramatic turn in the condition of the patients; jaundice disappeared completely in a short time and the patients recovered.

A review of the twelve cases of hepato-jaundice shows the following results. There is no need to emphasize that all cases were in a most serious condition and were poor risk cases. Some of them showed definite clinical signs of a beginning acute yellow atrophy of the liver. This clinical diagnosis could be confirmed at operation. Of these twelve cases, three died on the following day in hepatic coma, and one, a week later, in a shock following blood transfusion. The eight others recovered completely. These results must be evaluated in consideration of the fact that clinically all of them were believed to be in a rather hopeless state and that medical treatment has proved a failure.

The writer is not alone within these observations. For more than twenty years, similar cases have been reported (Schlegel, Laqua, Frangenheim, v. Haberer, Bergenfeldt). What is the pathologic meaning of these observations? *Obviously, the answer as to how the operation works, explains at the same time, the pathogenesis of hepato-jaundice.*

Here is a summary of the operative observations which any satisfactory theory of hepato-jaundice has to cover.

(1) The common duct is not dilated. (2) There is no increased back pressure in the duct. (3) The papilla can easily be passed with a sound. Spasms are sometimes observed but are only temporary and rare altogether. (4) The gallbladder is almost regularly distended, but empties its content on slight pressure freely down into the duodenum. (5) The bile in the gallbladder is sometimes very dark and inspissated; in other instances however, it is completely discolored and whitish. The bile in the ducts, was in the majority of my cases, replaced by a turbid whitish liquid with many precipitations of epithelial debris and some mucus. (6) Such debris was found also in the ampulla. (7) Biopsy specimen of the liver and post mortem ex-

aminations show that the intra-hepatic ducts and bile capillaries in some instances contained inspissated bile at an early stage of the disease. A most enlightening observation has been made by Barber and Osborn. These authors had the rare opportunity of studying the morbid anatomy of an acute icteric hepatitis on a man who through accident died in the first stage of the disease on the seventh day after development of jaundice. The following microphotogram illustrates both anatomy and functional state of the liver cells at the onset of the disease.

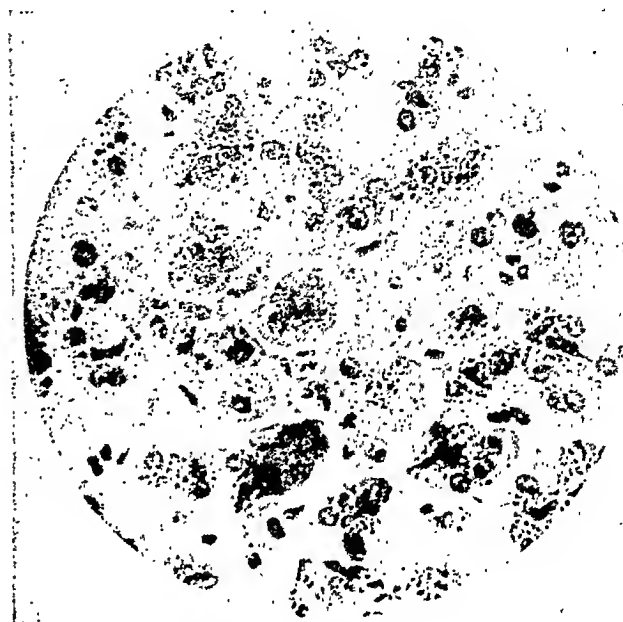


Fig. 2. — Numerous bile capillaries are prominently outlined by inspissated bile. Note coarse and fine granules of bile pigment in the liver cells. Taken from H. Barber and S. R. Osborn. *J. Path. and Bact.* 49:587, Nov. 1939.

"The liver cells were most affected near the central veins of the lobules. The nuclei of the cells show mitotic figures but more numerous than the mitotic figures were hyperchromatic nuclei, which had just completed division. In most parts, the bile-capillaries near the central vein were distended with inspissated bile. No bile was seen in the capillaries nor in the small bile-ducts at the periphery of the lobules. The bile ducts in the liver were well preserved, contained some uncolored mucoid fluid and were not inflamed." (Abbreviated report from the paper of H. Barber and S. R. Osborn).

These findings in my opinion demonstrate quite clearly that only the bile excretion from the liver-cells has completely stopped; the further expulsion of bile from capillaries in which a stasis and inspissation of the bile can be observed apparently has stopped as well. The complete block does not parallel the damage to the liver-cells which show definite signs of a rather increased activity in the appearance of mitosis and hyperchromatic nuclei. The intracellular production of bile-pigment obviously still goes on which due to the excretory block accumulates as coarse and fine granules within the cells.

(8) The liver cells are enlarged, filled with bile pigment and frequently show mitotic figures as a sign of activity in bile-production. (9) The second part of the duodenum is inflamed. In the initial stages, spastic conditions can be found while in the later stages a paralytic stasis develops. (10) The presence of painless duodenal ulcers without clinical history. (11) When opening the common duct or simply manipulating in this region, a drainage of bile sets in, sometimes dramatically, already on the operating table, in other instances within 24 hours, even when the bile drainage has completely stopped previously for six to eight weeks.

Obviously none of the above-discussed theories of the pathogenesis of hepato-jaundice, the least the one based on cell destruction, can cover and explain these numerous observations. The only concept I can think of which would cover all the facts is the following:

The dramatic onset of bile-drainage from the liver, provoked by simple manipulation on the duct system, strongly suggests a release of a *cellular excretory block* comparable to the onset of diuresis following decapsulation of the kidney or a sympathectomy.

Production of bile pigment (hepato-rubin) still goes on in the liver cells which show actually signs of increased activity (enlargement and mitotic figures). It can be considered now as a well-established fact that different functions of the liver cells are completely separated in time and intracellular or intrabubular geography (Forsgren, Giraudel, Elton).

Accepting this concept of a partial or complete cellular excretory block as the main cause for the development of hepato-jaundice, the following question arises: Is this block caused by a toxic damage directly to the very liver cell, or by way of the hepatic branches of the sympathetic nerves? The answer is given in my opinion by the other findings, especially those on the extra-hepatic duct system. The intracellular excretory block apparently is followed or associated with a paralytic dyskinesia of the whole biliary duct system.

Observations with cholangiography have taught us that the biliary duct system is not a system of rigid and motionless tubes, but has an active role in the expulsion of bile. It is not only the gallbladder which, with its contractions, is coordinated by a nervous regulating system with a timed opening of the sphincter of Oddi, but there are probably also coordinated movements in the intra-hepatic duct system and bile capillaries comparable with the movements in the blood capillaries. These movements, narrowing and widening of the lumina, are essential for a proper bile expulsion.* The first impulse for bile expulsion probably starts within the liver cell. It releases the motor action of the whole intra and extra-hepatic duct system, an irritation wave, which ends in the second part of the duodenum.

* They have been observed following injection of Choleretics.

We may imagine that the liver cells bordering the bile capillaries change their size with the expulsion of bile, and that the cellular contraction starts a kinetic impulse leading right down to the papilla. With the onset of an excretory block in the liver lobules, the whole excretory system is disturbed, resulting in a *general dyskinesia*. When operating on such cases we may observe the interesting fact that the common duct contains small amounts of normal and freshly secreted bile, which, however, is not expelled through the papilla, but trickles only now and then into the duodenum. The gallbladder is also unable to empty its contents through the patent cystic duct, while a slight finger pressure easily empties the gallbladder. Such a *paralysis of the bile duct system* answers the many rather puzzling questions which have been raised by many observers.

Among other things, it explains the regular observation that in hepato-jaundice *no B-Bile has ever been obtained*. When performing duodenal tubage the paralytic gallbladder does not contract and the liver cells, through the excretory block, cannot discharge their pigment stores.

There is, moreover, the interesting finding of a paralytic stasis in the second part of the duodenum. Soon after our first observation of a painless ulcer and duodenal stasis, we have frequently carried out X-ray examination of the duodenum in cases of hepato-jaundice.

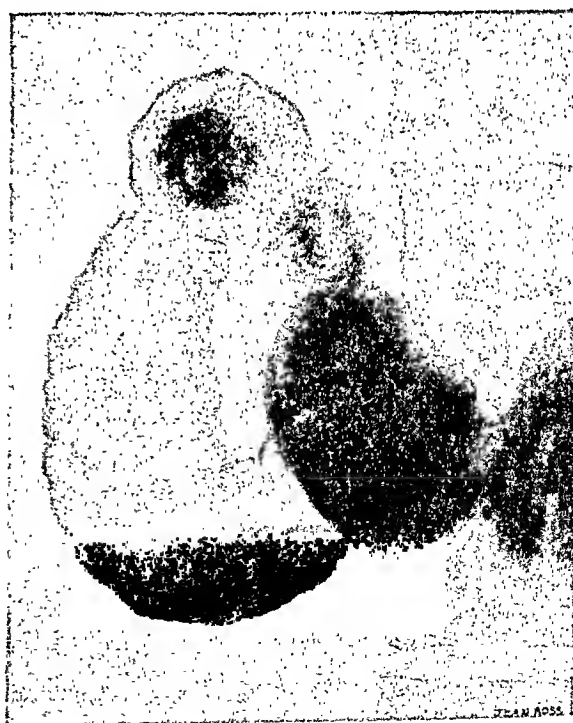


Fig. 3.

Our observations confirm similar observations of Pavel and his co-workers. Sometimes in the initial stages, a spastic irritation of the duodenum is found which, however, invariably passes into a *paralytic stasis*

of varying degree. Here I wish to mention an almost unique observation of H. Barber and S. R. Osborne, in the case already mentioned.

The duodenum was of normal size and contained much tenacious white mucus, no bile, but a number of droplets of bright metallic mercury. The patient drank the mercury droplets with a glass of water over which the nurse had broken a thermometer four days previously. No mercury could be found beyond the second part of the duodenum proving that the stasis had lasted for at least four days and was limited to this part only.

It remains the interesting observation of painless ulcers which suggest comparison with trophic ulcers.

When trying to bring all these pathologic changes over one common denominator, we find it only in the hepatic branches of the splanchnic nerve or perhaps its centers. In this respect, experiments of Brocard are of interest. Brocard succeeded in producing a hepatitis (sine ictero, however) by injecting minute, almost hemacopathic doses of phosphor oil (solution of phosphorus in oil) into the splanchnic nerve. *Parenteral* injection even of much higher doses did not cause similar damage.

The following changes could be observed in the liver. (1) Dilatation of the capillary veins. (2) Hyperplasia of the reticulo-endothelial cells.

Fatty degeneration	} in the liver cells
Cytolysis	
Pycnosis	
Insular necrosis	

The following observations support the role of the sympathetic nerves in causing the excretory block in the liver cells. Paravertebral injection of a 1/2% procaine solution between D10 and D12 may, in some cases of hepato-jaundice, provoke the sudden onset of bile drainage. (Fourteen cases observed by A. Dick). Personally, I had success, indeed a dramatic one, in one case of a patient in an almost precomatose state; operation was decided on but a trial with paravertebral injections of 20 cc. of 1% Procaine solution was made. The next day the stool was bile-stained for the first time in six weeks and the patient recovered. In other cases success was less pronounced and operation was performed.

How does the damage to the nerves or nervous centers in *infective hepatitis* take place? To answer this question we have to remember that viruses may have or may acquire some definite neurotoxic properties. We know this from the yellow fever virus which, after some passages, may become exquisite neurotoxic; we know this also from the virus of infective hepatitis. In some epidemics neurocerebral symptoms may appear right in the beginning. So the concept would be quite acceptable and compatible with all observations, that a certain toxic damage to the hepatic branches of the splanchnic nerve or its centers could be related to neurotoxic virus strains.

The surgical approach, initiated in the beginning by an erroneous diagnosis, has certainly contributed

observations which still have to be fully evaluated. Moreover, a new field is opened for operative treatment of cases of hepato-jaundice that are dragging on and will not improve under medical treatment. Operation is indicated especially in those cases which, through appearance of central-nervous symptoms, seem to take a dangerous turn to acute atrophy and hepatic coma.

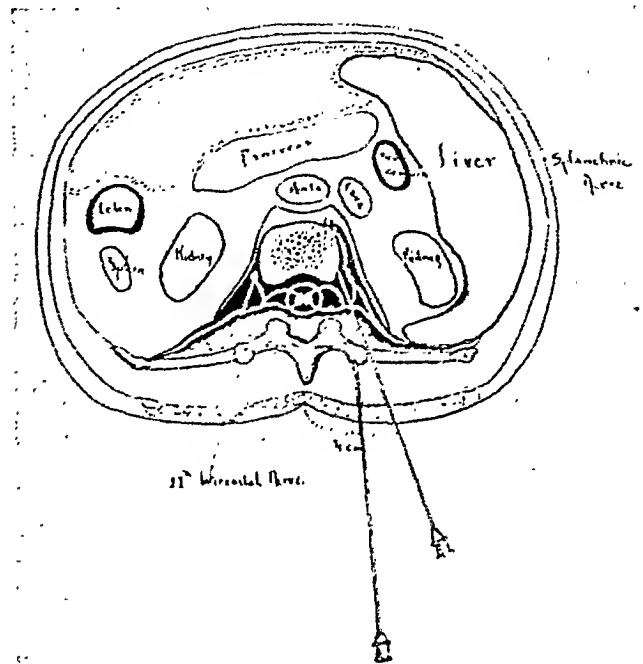


Fig. 4. — Technique of paravertebral injection for releasing the excretory bile-block in Hepato-Jaundice.

SUMMARY

In twelve cases of hepato-jaundice, some of them taking a turn to develop into hepatic coma after a long-lasting jaundice, operation for common duct drainage was performed. The diagnosis was uncertain; the indications were given through the sinking conditions of the patients and the failure of medical treatment.

In all twelve patients bile-excretion, which had been almost completely blocked for several weeks, started already on the operating table or within the next twelve hours. This release of the excretory block followed the opening the common duct, opening of the gallbladder or even simple manipulation around the common duct.

In three cases, a duodenal ulcer on the anterior wall of the duodenum was found that had not caused any clinical symptoms. One ulcer was painlessly perforated, apparently the day before operating. Two cases died on the day following the operation in unimproved hepatic coma. The patient with the ruptured ulcer died eight days after the operation in a shock following blood transfusion. The other eight recovered completely within a short time.

These observations, which conform with similar

ones reported in the literature, inspire a revision of the present theories of hepato-jaundice which do not cover and explain these observations.

Obviously, the answer as to how the operation works explains, at the same time, the pathogenesis of hepato-jaundice.

The following concept is presented.

Hepato-Jaundice is caused by a partial or complete cellular excretory block. In addition, a paralysis of the whole cholokinetic bile-duct system, including the gallbladder may develop. The paralysis includes

the second part of the duodenum, where atonic dilatation and stasis could be observed in X-ray examinations. The formation of painless ulcers of a trophic character in the second part of the duodenum has been observed in one-third of the operated cases, in one of them leading to a painless perforation. These facts can be explained only by the concept of a toxic damage to the neuro-centers of the hepato-duodenal branches of the splanchnic nerve. The damage might be caused by a neurotoxic virus-strain. The success of the operation would fall in line with the result of a block-releasing sympathectomy.

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Diarrhea

By

MICHAEL H. STREICHER, M.D.

CHICAGO, ILLINOIS

FOR SOME REASON the symptom of diarrhea often spells organic disease to the layman; yet many thousands of people remain chronically constipated yet presumably unconcerned about it. The patient is still more alarmed with the onset of diarrhea in view of the fact that he has always been constipated.

It is essential therefore that these various manifestations be interpreted to the patient in terms of fundamental physiological principles.

With this object in mind I thought it may be helpful to review some of these entities and also bring up to date some of the therapeutic measures recently attempted.

To make this discussion brief I will limit the present writing to the more common types of diarrheas of the infectious diseases of the colon and to diarrheas caused by impaired digestive secretion.

INFECTIOUS

A. AMEBIC COLITIS

In the consideration of the therapeutics of this entity, it is paramount to identify amebiasis as referring to the infestation in general and to amebic dysentery as a stage in the general process in which diarrhea is predominant.

The disease can be identified by an accurate and repeated search of ameba in specimens of fresh stools.

Clinically, one may be guided in the management of this disease by the presence or absence of blood in the stool, the disappearance of tenesmus, the recurrence of remissions, and the physical condition of the patient. Another index of adequate treatment is the improvement of the colon mucosa observed proctoscopically.

As one assumes responsibility in the care of this entity, it is essential to direct these patients to rest and to maintain good nutrition, supplemented by vitamin requirements; also to direct particular effort to live under hygienic conditions and thus avoid transmission of this infestation.

Before specific treatment is begun, one may treat patients symptomatically; that is, a diet of low residue high calorie and high vitamin should be prescribed; then the diarrhea can be checked by prescribing powdered opii gr. 1/2 (30 mgm.) in capsules to be taken after every third stool.

Supportive measures may also be instituted while specific treatment is being applied.

In spite of the good results that are obtained in the management of amebic infestations, it is nevertheless true that it is not devoid of serious complications such as liver abscess or abscess of the brain and lung.

The specific treatment is two-fold, based primarily on the clinical stage of the disease. In the vegetative stage (amebic dysentery) when diarrhea, tenesmus, and abdominal cramping is predominant, emetine hydrochloride is most efficacious. Given subcutaneously twice daily in doses of 30 mgm. for a period of 10 days, it has been noted to result in uniform relief of symptoms in 10 per cent of the patients. Concentrations of emetine required to be effective against ameba cysts are injurious to the host, therefore a large percentage of patients present stools positive for encysted forms of the parasite after a single course of treatment with the alkaloid. After a period of rest (seven days) the course of administration of emetine hydrochloride may be repeated.

Because of the cumulative property of this agent, toxic symptoms are frequent; therefore, it is advisable to keep the patient in bed during its administration.

The therapeutic agents most applicable in the chronic (encysted stage) are the iodine containing preparations and particularly chiniofon. This drug may be administered orally and the dose is four to eight grains given three times daily before meals for 10 days. After a rest period of seven days this routine may be repeated.

Craig (1934) and Chopra et al. (1937) state that chiniofon is preferable due to its low toxicity. Recently (1945) we have learned that sulfathalidine (phthalylsulfathiazole) may be administered as an aid in the treatment of amebiasis; although the new sulfonamide is not specific in these instances it appears to be of value "in that it minimizes the extent of the

ulcerative lesions by reducing the number of secondary invaders" and thus permits a clear avenue for approach by the amebicide.

Vioform and diodoquin contain 38% and 82% of iodine respectively; these preparations may be prescribed in four gr. doses three times daily for 10 days. They are less effective than chiniofon.

Emetine Bismuth Iodide has been used in capsules of three grains each for 12 days. The reports on the toxicity of this preparation have not been favorable.

Carbarsone has not been used very extensively in recent years, mainly because of the toxic effects reported in the literature. It is effective against ameba cysts and is administered in capsules of four grain twice daily for 10 days.

The usage of mercurial, silver, or arsphenamine preparations has long been discouraged.

B. CHRONIC ULCERATIVE COLITIS

It is well to clarify the terminology of this entity at the onset. This entity has often been referred to as "idiopathic" or "non-specific." In our opinion it is a bacterial infection but is not specific (Streicher and Kaplan 1930).

The patients often present themselves for treatment in the terminal stages of the disease. The early indication of impending disease is an increase in the number of evacuations daily, with presence of blood, moderate loss in weight, and straining at stools associated with tenderness in the left lower quadrant.

As the disease progresses, unchecked, the stools are increased to from 15 to 25 daily. There is blood, mucus and pus in each stool, with considerable griping in the left lower quadrant, tenesmus in the rectum, dehydration and a secondary anemia.

In the management of this disease one must also be guided by the proctoscopic findings in the colon, inasmuch as diet and medications are altered at various interval stages (Streicher 1938).

The treatment of chronic ulcerative colitis in general is dietary and supportive. It is essentially conservative and medical in scope. Surgical management of this entity is gradually disappearing from the literature (Streicher, 1942). With the development of the antibiotics, surgical treatment has been reserved entirely for extreme complications of the disease.

At the onset when the disease is in mild form the patient's symptoms may be controlled by a diet of low residue, high caloric and high vitamin content. If the diarrhea has progressed so that the number of evacuations are excessive, powdered opium gr. 1/2 (30 mgm.) may be employed in tablet form or in capsules; this may be given around the clock after every third stool.

After examination of stools has ruled out amebiasis, one may employ the newer bacteriostatic agents such

as succinyl sulfathiazole or by preference phthalyl-sulfathiazole (Streicher 1943 and 1945). The dose we suggest is two (.5 gm.) tablets three times daily before meals. This dose may be maintained for an indefinite period as far as toxicity is concerned. The other consideration in maintaining prolonged intake is the individual sensitivity of the patients to the particular sulfonamide. Our experiences with these antibiotics have been very favorable. These dosages may be maintained for two months uninterrupted and repeated at intervals after a rest period of two to three weeks.

In addition to the treatment described above, the patient's diet is supplemented by cevitamic acid of 50 mg. three times daily and by liver extract (two cc. given intramuscularly once or twice weekly).

Because of the extreme loss of chlorides in the stools we often observe a gastric subacidity in the patients as well as a dehydration. It is therefore that dilute HCl is often prescribed in doses of 10 to 15 drops three times daily after meals, or "acidogen" or "acidulin" in tablet or capsule form.

In terminal stages of the disease when blood lost in the stools reaches extreme proportions and considerable plasma protein is lost, it is essential to aid the patient with repeated blood transfusions and amino acids given intravenously or to use such substitutes as 1% saline and 5% glucose intravenously. When the patient recovers sufficiently to maintain a diet orally, it may be supplemented by a powdered protein such as aminoids or a protolysate.

Recently, we have had a good deal of experience with a new antibiotic used both intravenously and orally. I am referring to the use of penicillin in chronic ulcerative colitis (Streicher 1947). While its use is still in the experimental stage, we have had sufficient experience up to the present time to suspect that it may prove to be a very efficient and useful agent.

Another antibiotic recently added to our clinical trials is oral tyrothricin (spore free). The conclusion we reached at this stage of our research is that tyrothricin may be used orally with caution, and that apparently the fractional components of tyrothricin, namely gramicidin and tyrocidine are not toxic because the component substances are very largely destroyed in the intestinal tract. There is some evidence of hemolysis of erythrocytes when oral tyrothricin is administered to patients with far advanced ulcerative lesions in the colon, and for this reason I advise against its use at this time (Proceedings of the Central Society for Clinical Research Vol. 19, 1946).

In many instances it becomes necessary to treat the symptom of secondary anemia; it is well to point out that many patients do not tolerate iron preparations orally. In patients with ulcerative colitis iron medications tend to exaggerate the diarrhea and therefore the physician is obliged to supply the required needs of iron in form of foods.

As result of the repeated evacuations there occurs an infective proctitis and a pruritus; this may be alleviated by sitz baths of plain hot water taken once or twice weekly for 15 to 20 minutes each time. It is also helpful to apply a thin layer of aquaphor around the anus once or twice weekly at bedtime.

There is always much discussion about the allergic phenomena that may be present in these patients. It is very likely that some patients are sensitized to certain items of foods, but it is not our impression that this entity is purely of that etiology. Laxative foods and foods that may cause swelling of eyelids, or symptoms of angioneurotic edema should be omitted in the diet.

Much has been written about the psychogenic factor as being responsible for the onset of the disease, Backus (1944) or that emotional disturbances could be considered as important etiologic factors.

My own reaction in this matter is that while I do feel that a psychogenic factor or an emotional disturbance may at certain logical intervals influence the exacerbation or a remission of chronic ulcerative colitis I cannot conceive such factors as primary in a severe infectious process.

This disease is one of the most tedious and difficult to manage, and while the recent developments in the antibiotics have been very helpful, it will still require all the ingenuity in the possession of the doctor to maintain patients with ulcerative colitis in good health.

C. BACILLARY DYSENTERY

This ailment is an infectious process involving the colon and is caused by bacilli of Flexner, Shiga and Sonne.

The recent disease, while commonly found in the tropics, has been prevalent in recent years in the temperate zones. It has been shown that the infestations with the Shigallae dysenteriae are responsible for the extreme acute forms of the disease, that the Flexner types are of short duration, and that the Sonne infections are very mild and short-lived.

The disease in general is spread by poor sanitary conditions such as is prevalent in army camps with poor facilities for the disposition of excreta and with infected meat and polluted water supply. It has often been referred to as the "institutional dysentery."

Primarily, the patient presents himself for management because of an acute onset of severe abdominal cramping, and a diarrhea varying from 15 to 40 stools daily consisting of a bloody mucopurulent material. As the patient becomes dehydrated he loses considerable weight and becomes completely exhausted.

In our experience powdered opium gr. 1/2 may be used after every third stool to help check the diarrhea. At times we combine this with atropine sulfate gr. 1/150 given every six to eight hours during the acute phase of the disease, or substitute phenobarbital gr. 1 1/2 every six hours.

To combat dehydration and exhaustion intravenous medication of 5% glucose plus 3,000 cc. saline may be given every 24 hours for as long as needed. The diet is limited because the patient has numerous spells of vomiting; when tolerated it is composed of barley or rice water, tea with lime juice, soda crackers, mashed potatoes, cooked rice, toast, crackers, soft boiled eggs, boiled chicken and jello.

During the acute stage when the patient is exhausted and chilled it is essential to keep him warm and to apply hot moist dressings to the anus to relieve the tenesmus and to alleviate the local irritation of the buttocks. It is also helpful to apply heat to the abdomen.

The therapeutic value of serum therapy is questionable. Felsen claims that the use of human convalescent serum has been of advantage during epidemics. Flexner is of the opinion that serum therapy helps reduce the mortality in bacillary dysentery by one-third. In the case of the Shiga and Flexner types, sulfasuxidine has been reported to produce best results by Marshall, Lyon, Cooper and Libby; the Sonnei type however is treated more adequately with sodium sulfathiazole and sulfadiazine. Favorable results have been observed with sulfaquainidine.

Manson-Bahr is of the opinion that irrigations or instillations of therapeutic medications by rectum are of limited value. The complications which are noted in the chronic stage of the disease are urinary infections, local infections in the rectum, arthritis and infections of the eye. These are treated symptomatically.

Prophylaxis is apparently the factor most important in the management and control of bacillary dysentery.

II. IMPAIRED DIGESTIVE SECRETION

A. ACHYLIA (GASTROGENIC DIARRHEA)

Ordinarily the absence of free hydrochloric acid is compatible with good health and produces no untoward symptoms in the gastro-intestinal tract. At times dyspepsia and diarrhea may ensue.

The diarrhea is produced because in achylia, the food (undigested) remains in the bowel as an irritant. In addition to obtaining a gastric analysis under histamine stimulation careful evaluation of the blood picture should be made.

Absolute achylia is observed in pernicious anemia, alcoholic gastritis and syphilis of the stomach; the blood picture, however, in alcoholic gastritis and syphilis of the stomach is that of a secondary anemia.

To check the immediate symptom of diarrhea, regardless of the etiology, 15 drops of dilute hydrochloric acid may be administered three times daily before meals or 15 minutes after meals for many weeks if necessary; this should be supplemented with a diet of low residue, high calory and high in vitamin B₁ content.

If the blood picture is that of a pernicious anemia, liver extract intramuscularly and blood transfusions are indicated. Iron compounds which are commonly prescribed in secondary anemias are not well tolerated in patients who have diarrheas; the number of evacuations are exaggerated on oral intake of iron compounds. One therefore has to rely on iron containing foods and liver extract given intramuscularly

to alleviate the symptoms of secondary anemia in patients who have a severe diarrhea due to gastric achylia.

B. BILIARY DEFICIENCY

The absence of bile salts in the small intestine may produce a disturbance in the digestion of protein, an increase in the transport of food through the small intestine because of the presence of large volumes of unabsorbed fat, and an intestinal putrefaction.

Additional findings may be associated (depending on the etiology) such as an acholic stool, a diarrhea, a moderate degree of jaundice, vomiting and a moderate loss in weight.

Much of the fat ingested is lost in the stool in the form of unabsorbed fatty acids, calcium soaps and unemulsified neutral fat.

Primarily the treatment is directed towards the removal of the source of biliary obstruction.

When such methods are not possible and prove impracticable symptomatic or supportive measures are adopted. A diet is prescribed which is high in protein and carbohydrate but low in fat. Amino acids have been used extensively to supplement the diet. Vitamin K given orally in doses of one mg. three times daily may be used to advantage. Vitamin A, B and C and D should also be used. Blood transfusions have been recommended when marked liver damage is associated. Calcium compounds given orally have also been used, but are of doubtful value. In general these therapeutic measures are temporary in scope.

C. PANCREATIC DEFICIENCY

Pancreatic insufficiency has been referred to in the literature as pancreatic achylia of Einhorn.

Disease of the pancreas is usually suspected when one presents the findings of a large liver, a moderate loss in weight, a diarrhea, a secondary anemia and possibly a jaundice which is persistent but unassociated with pain.

If a tumor is suspected, X-ray studies of the gastro-intestinal tract will reveal a filling defect on the greater curvature of the stomach corresponding to the area occupied by the pancreas.

The stools are light colored, bulky, foamy, and contain large amounts of neutral fat (steatorrhea).

The therapeutic outline suggested by Beazell, Schmidt and Ivy (1941) is the most satisfactory; four grams of enteric coated tablets of pancreatin are used before and after each meal. This dose corresponds approximately to 15% of the twenty-four hour output of pancreatic juice. In addition bile salts may be administered. Vitamin B complex and Vitamin A are usually lacking and should be supplemented. Dilute hydrochloric acid is also added when gastric achylia is present; thirty drops may be administered at each meal. The diarrhea is curtailed on addition of dilute hydrochloric acid.

A diet is prescribed consisting essentially of moderate amounts of protein and carbohydrate but little fat.

In general the conservative management of malfunction of the pancreas is palliative.

Abdominal Apoplexy

By

WILLIAM SAPHIR, M.D., F.A.C.P.

CHICAGO, ILLINOIS

SPONTANEOUS HEMORRHAGE within the peritoneal cavity is not too uncommon. However, if bleeding of genital origin in females and bleeding due to trauma are excluded spontaneous hemoperitoneum is a rare incident. It is this spontaneous intraperitoneal hemorrhage due to rupture of an intra-abdominal blood vessel, independent of any trauma to the abdomen, that has been termed "abdominal apoplexy" (1). Berk and associates (2) up to 1941 have collected only 21 cases (including their own) of such intra-abdominal apoplexy. Marks and Freedlander (3) in 1945 reported a total of 26 instances in 25 patients to which number they added three additional cases.

Berk and associates (2) advise that this catastrophe be considered in all patients in whom there occurs sudden severe abdominal pain, shock and signs of peritoneal irritation, especially in the presence of hypertension. Early operation, with ligation at the bleeding point is the only treatment offering a chance of recovery. Unfortunately, nothing pathognomonic, in either symptoms or signs has been noted in their cases to permit a definite pre-operative diagnosis. Inasmuch as mesenteric arteriosclerosis is considered the most common underlying process responsible for the spontaneous rupture of an artery supplying an abdominal viscus (1) knowledge of the symptomatology of mesenteric arteriosclerosis would aid in pre-operative diagnosis. Unfortunately, little is known about the symptomatology of mesenteric arteriosclerosis prior to such catastrophic events. The clinical symptoms are few and ill defined. Vague digestive disturbances, the mild diabetes mellitus of the aged, achlorhydria, intestinal atony and obstipation are mentioned as direct or indirect results of mesenteric arteriosclerosis (4).

It is the purpose of this paper to report an additional instance of abdominal apoplexy, to emphasize the obscurity of symptomatology of mesenteric arteriosclerosis and particularly to point at the striking similarity of colonic neurosis to organic mesenteric arteriosclerosis.

CASE REPORT

Mr. S. G. age 42, came to the author's attention in 1934 presenting a history of recurring bowel distress of a few years duration. Episodes of cramping, griping pain in the lower abdomen, distention and bloated feeling lasting for days or weeks intervened between varying periods of freedom from bowel dysfunction. As a rule, constipation prevailed but during periods of abdominal

distress irregular and loose bowel movements occurred. Occasionally mucous discharge was noted in excreta but at no time was there either frank diarrhea or melena. Physical examination revealed a thin, asthenic and obviously undernourished individual presenting evidence of vasomotor instability, as flushing of skin, moist hands, dermatographia, and slight tremor. Heart and lungs were normal. The abdomen was soft and slightly distended. There was minimal tenderness over the ascending and descending colon. Liver and spleen were not palpable. Blood pressure, blood count, Kohn test, and urinal examination were all within the limits of normal.

The patient appeared emotionally disturbed and upon questioning related numerous difficulties in his marital life and economic status. It was during periods of mental stress that episodes of bowel dysfunction became particularly noticeable.

Subsequent laboratory tests including a gastro-intestinal X-ray series, bacteriologic examination of the stool, proctoscopic examination, basal metabolism determination, and agglutination tests for enteric antigens, were all essentially negative. A diagnosis of irritable colon (colonic neurosis) was made.

During the following eight years, the patient's condition remained essentially unchanged. Periodic exacerbations were treated with antispasmodics, phenobarbital, and dietary measures. During the war years the patient was not seen by the writer. After an interval of three years the patient presented himself proudly pointing to marked improvement in his social and economic status. His wife, formerly estranged, had returned to him. There was nothing to disturb him mentally. Yet, his physical condition had not changed. Abdominal discomfort and colonic dysfunction had continued intermittently as before. Physical findings and laboratory tests were essentially as normal as on previous examinations.

On the sixth of May 1946 the patient suffered a sudden attack of agonizing abdominal pains and vomiting. When seen, the patient was obviously in shock. There was pallor and perspiration, a blood pressure of 90 over 70, a pulse rate of 120 and no fever. The abdomen was moderately distended and soft. There was marked tenderness over the peri-umbilical region and lower mid-abdomen. Bowel sounds were audible. Liver and spleen were not palpable. The patient was immediately hospitalized. The red blood count was 3,670,000, and hemoglobin 10 gms, white blood count 22,400 with 82 per cent polymorphonuclears. An abdominal X-ray flat plate revealed absence of free air. A surgical consultant advised expectant management. During the next few days pallor and anemia increased. The patient became restless and complained of severe abdominal pains and nausea. The abdomen remained soft. Significant localizing signs were absent. Opiates, intravenous glucose and blood transfusions did not seem to influence the downhill course. On the third hospital day signs of flous with increasing abdominal distention and disappearance of bowel sounds became manifest. Coincidentally, the temperature rose to 100.4, the blood pressure rose to 180/110 and the previously negative urinal showed marked albuminuria. Finally, sudden paralysis and paresthesias of the right

From the Department of Medicine, Michael Reese Hospital, Chicago, Illinois.

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leg with appearance of skin suffusions in right lower abdomen and upper thigh occurred. Pulsation of the right femoral arteries disappeared. The patient died five days after hospital admission.

Autopsy. (abbreviated). Upon opening the abdominal cavity approximately 2000 c.c. of fluid and clotted blood were found. The mesentery was hemorrhagic, the mesenteric layers infiltrated by old organized and more recent blood clots. The superior mesenteric artery revealed a dissecting aneurysm with clotted blood separating the intima from the media. There was hemorrhagic infiltration of the intestinal serosa. The gastro-intestinal tract otherwise appeared grossly normal. There was a marked generalized arteriosclerosis, with involvement of coronary arteries and subsequent myocardial fibrosis. The aorta presented numerous arteriosclerotic plaques, ulcerated in part with the formation of small atheromatous cavities and subintimal dissections in its descending part. The left renal artery was the seat of a two cm. dissecting aneurysm with separation of intima and media by clotted blood having produced a marked narrowing of the lumen of the vessel at this point. A similar lesion though less extensive, was found in the right renal artery. There was a considerable amount of clotted blood in the retroperitoneal region, encapsulating each kidney and infiltrating in the right inguinal ring and testicle. Hemorrhagic infarcts were observed in the left kidney.

Comment. This patient presented the typical symptoms of the irritable colon syndrome (colonie neurosis) for many years. The final episode and autopsy findings demonstrated the presence of severe mesenteric arteriosclerosis. Death was due to rupture of an arteriosclerotic dissecting aneurysm of the superior mesenteric artery producing the clinical symptom complex of abdominal apoplexy. Coincidentally, an arteriosclerotic aneurysm of the left renal artery had led to dissection and marked narrowing of the vessel probably accounting for the terminal hypertension and albuminuria. Finally, a retroperitoneal hematoma resulting from the rupture of the aneurysm of the renal artery contributed to the fatal outcome.

DISCUSSION

Mesenteric arteriosclerosis is a neglected subject at present as compared with arteriosclerosis of other vessels, notably the coronary arteries. Leading textbooks devote little space to the existence of mesenteric arteriosclerosis and to its obscure symptomatology. It is not mentioned in the differential diagnosis and the etiology of the irritable colon (1, 4, 5).

In recent years, psychosomatic medicine has attained great influence upon medical teaching and thinking. Once the diagnosis of irritable colon is made it is treated as a functional neurosis. Such a concept is in distinct contradiction to that of a generation ago when Nothnagel (6) in his textbook denied entirely the existence of intestinal spasms as a purely functional neurosis. Could it be that the pendulum of psychosomatic medicine is swinging too far? Certainly, our case demonstrates the existence of severe organic arterial disease in what seemed a purely functional neurosis. It is readily admitted that the diagnosis of "irritable colon" is made only when organic bowel disease can be ruled out, but in view of our present inability to diagnose mesenteric arteriosclerosis accurately it follows that this condition should be seriously considered in the etiology and differential diagnosis of the irritable colon syndrome.

SUMMARY

A case of abdominal apoplexy is here reported and added to the few described in the literature. The underlying pathology was mesenteric arteriosclerosis. During an observation period of 12 years the clinical symptomatology was indistinguishable from that of the "irritable colon" syndrome. Mesenteric arteriosclerosis should seriously be considered in the etiology and the differential diagnosis of the irritable colon syndrome.

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The Use of Tripelennamine Hydrochloride (Pyribenzamine) as a Topical Anaesthetic

By

VINCE MOSELEY, M.D.*

CHARLESTON, S. C.

THE PHARMACOLOGICAL PROPERTIES of Tripelennamine hydrochloride (pyribenzamine hydrochloride N. N. R.)* are such as to make this drug a valuable adjunctive measure in the relief of pruritus or discomfort in many conditions other than those of an allergic nature.

It has previously been reported that the drug has considerable symptomatic, antipruritic and analgesic activity when locally applied to various types of dermatitis and to the anal mucosa (1).

It is also capable of producing local anaesthesia when placed on the cornea of a rabbit (2). These observations and the personal experience, after tasting a tablet of the drug and noting the prompt and rather long lasting local anaesthesia produced on the tip of the tongue and of the anterior mucosal surface of the roof of the mouth, led to a clinical trial of the drug as a topical anaesthetic for anaesthetization of the oral and pharyngeal mucosa.

I am unaware of any previous reports on the use of the drug for this purpose.

In all 30 patients have had their oral and pharyngeal mucosa anaesthetized by means of the local application of this drug prior to gastroscopy. The results were most satisfactory in each.

The anaesthetic effects were obtained by having the patient gargle and wash the mouth repeatedly with a 1% aqueous solution of Tripelennamine hydrochloride. The amount being limited to two portions of 10 cc. each. Each patient was instructed to agitate this amount of liquid about in the mouth and then gargle repeatedly with it, the solution being retained in the mouth and pharynx for periods lasting over three minutes. After this period of time the patient was instructed to expectorate the solution and after a four to five minute rest period the process was repeated for another three minutes of mouth rinsing and gargling. At the conclusion of this second period of gargling it was observed in all patients that anaesthesia of a degree sufficient to permit the easy passing of a gastroscope was present. The anaesthetic

*From the Department of Medicine, Medical College of the State of South Carolina and Out Patient Clinic, Roper Hospital, Charleston, S. C.

*The Tripelennamine hydrochloride used in these studies was very kindly supplied for this purpose by the Ciba Pharmaceutical Products, Inc.

effects lasted sufficiently long in all instances to permit full and complete examination of the stomach and removal of the gastroscope without pharyngeal discomfort or excessive gagging. The use of Tripelennamine hydrochloride has been as effective as any of the previously employed topical anaesthetics, used at this clinic in conjunction with gastroscopic examinations.

In addition to using the drug for this purpose it has also been used five times in apprehensive patients with very sensitive gag reflexes to allay their fear and discomfort during the passage of a gastric tube.

In two instances where extreme discomfort was present because of aphthous stomatitis the patients were instructed to rinse their mouths briefly with an aqueous solution of 1% Tripelennamine hydrochloride 15 minutes prior to eating. Excellent relief resulted and food ingestion was possible, when this had been previously almost impossible because of the severe pain.

Two patients with severely painful throats due to acute follicular tonsillitis were enabled following the topical use of this medication to obtain relief of sufficient degree to drink fluids and take oral medication with more ease than their pharyngeal discomfort had previously permitted.

One patient with a very painful carious tooth was given immediate relief of the pain by placing in the cavity a small amount of the drug in powder form.

Two patients with painful hemorrhoids, one of whom in addition had a fissure in ano, were treated symptomatically by local application of the drug in 2% strength in a water soluble ointment base. Anaesthesia of a degree sufficient to permit adequate rectal examination was obtained in each and relief for a period of 90 to 120 minutes was experienced after each application.

Although the drug is very bitter, it anaesthetizes so quickly that as yet no patient has complained because of this when used for oral or pharyngeal anaesthesia. It has not been observed in any instance, as yet, to produce nausea or vomiting. Salivation in excess of that observed with another frequently used topical anaesthetic has been observed, but this has not been so excessive as to cause any inconvenience in gastroscopic examinations.

Five healthy medical students were tested for their

reactions to the drug as to taste and any other unpleasant effects they might note from its local use. In each, the bitter taste, they were instructed to watch for, subsided in 30 to 45 seconds.

In two the solution was given in 1/2% strength and in two it was given in 1% strength. One of each two was instructed to rinse the solution in the mouth for only one minute and then expectorate it. The other two were instructed to retain it for two full minutes.

The loss of the bitter taste occurred at about the same time with each. No significant differences as to the time of the onset of the anaesthesia or the disappearance of this effect were noted by any of the four subjects.

In each of the four subjects demonstrable numbness of the tongue and oral mucosa was present in 2 1/2 minutes with good anesthesia in four minutes.

In 25 to 30 minutes all were subjectively and objectively aware of returning sensation to the oral and pharyngeal mucosa. In the fifth subject a swab moistened with 1% aqueous solution of Tripelennamine was applied for ten seconds to the left side of the tip of his tongue and to the right lateral border of his lower lip. In four minutes after this brief application the tongue area was objectively anesthetic to pin prick as was the lip. Both regions progressed to this point of sensory loss at the same rate. After 13 minutes some recession of the anaesthesia was noted in the tongue and at 15 minutes an equal degree of return of sensation had occurred in the lip.

None of the five subjects observed any unpleasant effects or side reactions.

These observations indicate the rapidity with which this substance, when in either 1/2% or 1% strength in an aqueous solution, can produce anaesthesia when applied to the oral mucosal surfaces and the duration for which such anaesthetic activity persists after only brief periods of application.

In patients in whom it was used prior to gastroscopy, anaesthesia of a degree sufficient to suppress the gag reflex persisted for 45 minutes to 90 minutes. This is more than an ample period of time in which to accomplish this type of examination. In the two patients with painful rectal lesions anaesthetic effects persisting for 90 to 120 minutes were observed after the local application of a 2% water soluble base ointment.

To date no undesirable side reactions or unpleasant effects have been observed from the use of this drug as a topical anaesthetic.

There are many instances which arise in the practice of medicine where a safe, efficient topical anaesthetic is of value in the symptomatic management of a patient or where such effects may be desired prior to instrumentation for diagnostic or therapeutic reasons.

Tripelennamine hydrochloride has anaesthetic properties that permit it to be employed for this purpose when anaesthesia for periods of 45 to 90 minutes is desired. With further observation it may prove safer to use this drug for this purpose than to use some of the now more generally used topical anaesthetics.

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The Inhibition of Lysozyme Activity

By

JACK N. MOSS

and

GUSTAV J. MARTIN, Sc.D.

PHILADELPHIA, PA.

MEYER, ET AL. (1) demonstrated large quantities of lysozyme in human gastric juice taken from patients with peptic ulcers. The lysozyme content decreased when the vagus nerve was cut.

Meyer et al. (1) also reported the effect of lysozyme on the "Pavlov pouch" of an anesthetized dog. When the enzyme was dissolved in the gastric juice, it was capable of removing the surface mucosa of the pouch. This in turn resulted in the formation of a small ulcerative lesion. It was therefore suggested that lysozyme might be an important factor in the etiology of peptic ulcers.

The inhibition of lysozyme activity has been demonstrated by Meyer et al. (1) with dodecyl sulfate. Lawrence and Kingel (2) were able to produce a marked inhibition of the enzyme with several derivatives of sulfonamides. Neter (3) brought about the inhibition of lysozyme with certain sulfamido compounds.

Research Laboratories, The National Drug Company, Philadelphia, Pa.

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The present communication deals with the effect of a series of materials, varying in chemical nature, upon the lytic properties of lysozyme. The importance of these observations in the field of gastroenterology is apparent.

EXPERIMENTAL

The inhibition of lysozyme activity was demonstrated on *Micrococcus lysodeikticus*, in accordance with a modified method described by Smolens and Charney (4). Since lysozyme acts over a pH range of two to nine (5), most of the substances were dissolved in the respective buffers covering this range. The adsorbing agents and resinous materials were tested in a medium of N/10 HCl which contained various amounts of lysozyme.

The following materials have been tested for "antilysozyme" activity and were negative: Cholic acid, rattlesnake venom, mnicin, atropine sulfate, phenobarbital, ascorbic acid, esenletin, hesperidin, heparin, hesperidin-ascorbic acid, hesperidin methyl chalcone, hesperidin methyl chalcone-ascorbic acid, salicylic acid, suramin, rutin, glucuronic, "menadione", salmine sulfate,

TABLE I
Lysozyme Inhibitory Action of Surface Active Agents

Compound	Concentration mgms/cc.	Lysozyme Units/cc.					Compound Control (No Lysozyme)
		500	250	125	62.5	31.25	
No. I Sodium alkyl sulfates	1.0	0	0	0	0	0	0
No. I Sodium alkyl sulfates	0.1	†	P	0	0	0	0
No. II Decyl benzene sodium sulfonate	1.0	0	0	0	0	0	0
No. II Decyl benzene sodium sulfonate	0.1	†	†	†	0	0	0
No. III N(acylcolumbiformyl)-methylpyridinium chloride	1.0	†	AC	AC	0	0	0
No. III N(acylcolumbiformyl)-methylpyridinium chloride	0.1	AC	AC	0	0	0	0
Lysozyme † culture control		†	†	†	†	†	
Culture control (no lysozyme)	0.0						

† — complete lysis
AC — almost complete lysis
P — partial lysis
0 — no lysis

protein hydrolysates, 7-methylfolic acid, desoxy-*pyridoxine*, 5-methyltryptophane, *ethionine*, α -amino phenylethane sulfonic acid, α -amino phenylmethane sulfonic acid, α -aminoisobutane sulfonic acid, imidazole aminomethyl sulfonic acid, oxythiamine, desthiobiotin, *p*-fluorophenylalanine, polyamine resin, sodium aluminum silicate, fuller's earth, diatomaceous earth.

The following showed slight activity: Sodium taurocholate, dicumarol, sulfonated hesperidin, phosphorylated hesperidin, and sulfonated coal.

Since dodecyl sulfate was shown to inhibit lysozyme, the activity of the anionic detergents (No. I and II) was expected. It is interesting, however, to note that cationic detergents such as No. III are capable inhibitors of lysozyme. The mode of action of compounds of this type warrants further study.

From the group of adsorbing agents a synthetic zeolite, an activated carbon, and hydrated aluminum silicate (Bentonite) were the best inhibitors of lysozyme under the conditions of the experiment (see Table II).

TABLE II

Lysozyme Inhibitory Action of Adsorptive Materials
(Materials Tested in Presence of 200 Units Lysozyme/cc.)

Compound	Concentration mgms./cc.	Lysis	Compound Control (No Lysozyme)
"Synthetic zeolite"	50	0	0
"Synthetic zeolite"	25	†	0
"Synthetic zeolite"	10	†	0
"Activated carbon"	10	0	0
"Activated carbon"	2	†	0
Hydrated aluminum silicate	10	0	0
Hydrated aluminum silicate	5	0	0
Hydrated aluminum silicate	1	0	0
Hydrated aluminum silicate	0.5	†	0
Lysozyme control (200 U/cc.)		†	†
Culture control (no lysozyme)		0	0

As shown in Table II, hydrated aluminum silicate (Bentonite), proved to be a remarkable inhibitor of lysozyme at comparatively low concentrations. This property was tested in a medium of gastric juice. Two hundred units of Lysozyme were added to each cc. of gastric juice. (The amount of lysozyme already present was not titrated). The results are given in Table III.

Various combinations of adsorbing agents were tested in the lysozyme system. One combination which proved very effective was that of Bentonite synthetic zeolite and a polyamine resin. A definite synergistic action was noted when the three materials were added at concentrations which were ineffective when tested singly (Table IV).

The relationship between lysozyme and formation

TABLE III

Lysozyme Inhibitory Action of Bentonite in Gastric Juice
† 200 U Lysozyme/cc.

Mgms./cc. Bentonite	Lysis	Bentonite Control
10	0	0
5	0	0
2	†	AC
1	†	0
Gastric Juice Control (Without excess lysozyme)	†	†
Lysozyme Control	†	†
Culture Control	0	0

TABLE IV

Lysozyme Inhibiting Action of Combinations of Adsorptive
Materials (200 Units Lysozyme/cc. in N/10 HCl)

Compound	Concentration Mgms./cc.	Lysis
Bentonite	0.5	†
Permutite	5.0	†
Polyamine Resin	5.0	†
Bentonite	0.5	
†	†	AC
Synthetic Zeolite	5.0	
Bentonite	0.5	
†	†	†
Polyamine Resin	5.0	
Permutite	5.0	
†	†	†
Polyamine Resin	5.0	
Bentonite	0.5	
†	†	
Synthetic Zeolite	5.0	0
†	†	0
Polyamine Resin	5.0	
Lysozyme Control		†
Culture Control		0

of peptic ulcers is a project which is still in its experimental stages and requires further study. However, the inhibition of this mucoid hydrolysing enzyme might prove to be an important factor in the treatment of gastric ulcers. Effective antilysozyme activity might result in the discovery of important therapeutic agents for peptic ulcers.

SUMMARY

1. A series of inorganic and organic compounds was tested in order to determine their effect on the lytic properties of lysozyme.
2. Under the experimental conditions presented, the following materials were active inhibitors of lysozyme: sodium alkyl sulfates, decyl benzene sodium sulfonate, *N*(acylcolaminoformylmethyl pyridinium) chloride, a synthetic zeolite, an activated carbon, and a hydrated aluminum silicate (Bentonite).
3. A combination of Bentonite, a synthetic zeolite, and polyamine resin displayed a synergistic action as lysozyme inhibitors.

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Idiopathic Megaduodenum: Report of a Case

By

J. E. McCLENAHAN, M.D.

and

BERNARD FISHER, M.D.

PITTSBURGH, PA.

DUODENAL DILATATION due to either extra or intraduodenal obstructive phenomena occurs occasionally. Much rarer, is dilatation with no apparent cause. A brief review of the literature, together with the report of a case of idiopathic duodenal enlargement, is presented.

Causes of duodenal obstruction may, for academic purposes, be classified as congenital and acquired (1).

Congenital Extrinsic Causes are: (a) peritoneal bands and adhesions (2); (b) malrotation of the gut (3); (c) annular pancreas (4); and (d) aberrant mesenteric vessels (3, 5, 6). The latter is the most common in this group. Due to redundancy of the superior mesenteric vessels in asthenic individuals, these vessels lie across the third portion of the duodenum producing a "band-like" effect with resultant obstruction and dilatation.

Congenital Intrinsic Causes are: (a) atresia; (b) stenosis; and (c) so-called "duodenal diaphragm" (7, 8). These types of obstruction have been attributed to improper embryologic development. Normally the primitive gut closes solidly when the embryo reaches five weeks. This obliteration of the lumen is due to a proliferation of epithelial cells. Later, vacuoles occur between these proliferating cells. These vacuoles coalesce resulting in complete recanalization and restoration of the lumen. Whenever faulty resolution of these epithelial cells occurs, stenosis, atresias and "congenital diaphragms" will result. They are manifested, clinically, chiefly at infancy and early childhood.

Acquired Extrinsic Causes of obstruction (9) might be (a) adhesions secondary to inflammatory processes, such as chronic cholecystitis; (b) post-operative adhesions; and (c) tumors of surrounding organs, as lymph-nodes and retroperitoneal tissue.

Acquired Intrinsic factors might be (a) carcinoma;

* From Department of Surgery, Mercy Hospital, Pittsburgh, Pa. and University of Pittsburgh, Medical School.

(b) lues; (c) tuberculosis; (d) jejunal ulcer; (e) foreign bodies; and (f) benign tumors, as adenomas.

Very rarely will duodenal dilatation occur with no extrinsic or intrinsic congenital or acquired factor producing it (10). Such a case, in an infant, was first reported in 1919 by Dubose (11). Aside from the case reported by Balfour and Gray (12) in 1932, in a man, the six cases reported by Kraas in 1933 (13) and a scattered few in which the etiological factors were indefinite (14, 15), little or no mention of this condition is made in the literature.

It has been suggested that this is akin to congenital megacolon or Hirschsprung's Disease and is due to faulty intrinsic nervous mechanism of the duodenal portion of the bowel. Thus, it has been called megaduodenum or congenital megaduodenum. However, histological studies of myenteric plexuses, when done, have been normal. So probably, until definitely proven, the term "idiopathic megaduodenum" would be more apropos at this time in the choice of nomenclature.

CASE REPORT

A 23-year old white male army veteran was admitted to the Mercy Hospital, Pittsburgh, Pennsylvania, on December 31, 1947, in no acute distress. His chief complaint was that he "felt tired and run down" for several months. He noticed tarry stools almost continually since December 12th or 13th, 1947, but paid little attention to this, continuing his work as a laborer. On December 27, 1947, he had a moderate hematemesis and was put to bed by his family doctor. After four days at home, he was admitted to the hospital. At no time previously had he had bouts of vomiting, food intolerances, or other symptoms referable to his gastro-intestinal tract. His family and personal history were non-contributory. Past medical history was negative, except for an accident suffered, while in the Army, in July 1944, when a truck ran over his chest fracturing several ribs. After a period of hospitalization he was returned to active duty.

Physical examination: on admission revealed a well-developed, asthenic, pale, young adult who, aside from some tenderness in the epigastrium, was perfectly normal.

Laboratory Data: RBC 3,650,000; hemoglobin 68% (10.5 gms.); NPN 28.9 mg.%; BUN 12.8 mg.%; Bl. sugar 84 mg.%; urinalysis was normal.



Fig. 1. — (a) Stomach (b) Duodenum (with fluid level)

X-ray following ingestion of barium meal revealed a normal esophagus and stomach, marked dilatation of the duodenum with an ulcer just distal to the pylorus. (See Figs. 1 and 2; Fig. 1 showing the cascading of barium from the stomach into the duodenum). Due to the extreme dilatation and because of the bleeding, it was decided to explore the abdomen. After pre-operative preparation with vitamins, whole blood and saline solution, on January 15, 1948 he had a laparotomy.

The abdomen was opened through a high right rectus incision. The abdominal viscera were entirely normal, except for the duodenum. This was markedly dilated throughout its first three portions, gradually tapering off in diameter so that at the ligament of Treitz it was perfectly normal. The first and second portions were as large as the stomach itself. A thorough search was made for any obstructive factor. The gastro-colic omentum was partially divided to explore the retroperitoneal duodenum. No bands, adhesions, or any of the previously mentioned etiologic factors were found. The ulcer crater seen on X-ray was found about one inch beyond the pylorus on the posterior wall. The crater was large enough so that the tip of the index finger could be inserted. A gastric resection was performed, removing two-thirds

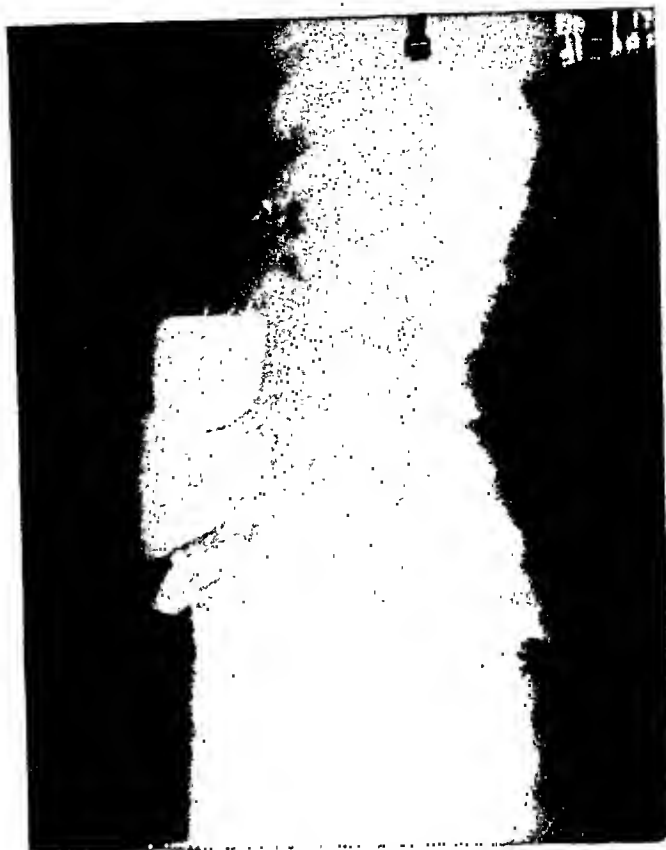


Fig. 2. — (a) Stomach (b) Duodenum

of the stomach, and a Poly, anti-colic anastomosis was performed.

The patient made an uneventful recovery from surgery and went home on the fifteenth post-operative day. At present, two months after the operation, he is in good health and doing light work.

COMMENT

Of approximately 250,000 admissions and 3,500 autopsies in the last twenty-five years at the Mercy Hospital, this is the only case of proven megaduodenum where no etiologic factor could be found. Except for the development of a bleeding ulcer, this young man may have lived his entire life unaware of this abnormality.

SUMMARY

A case of idiopathic megaduodenum, together with a brief discussion, has been presented because of the extreme rarity of the condition, there being only approximately a dozen such cases reported in the literature.

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NUTRITION

Nutrition and Efficiency

By

FREDERICK HOELZEL

CHICAGO, ILLINOIS

AT THE BEGINNING OF THE PRESENT CENTURY, it seemed that fletcherism, the practice of eating according to the principles advanced by Horace Fletcher (1, 2, 3), would solve the nutritional problems of man, greatly increase physical efficiency and prolong the life span. The claims made by Fletcher largely stimulated the study of the minimum protein requirement of man which was made by Chittenden (4). Fletcherizing (masticating food thoroughly) was enthusiastically promoted at the Battle Creek Sanitarium by Dr. John Harvey Kellogg. Fletcher's claims were more or less supported by the results of tests made on students by Irving Fisher (5). Fisher (with Fisk) also helped to popularize fletcherism through over 20 editions of *How To Live*. As late as 1922, Holck began a five-year test of "modified fletcherizing" at the University of Chicago (6). However, fletcherism apparently reached its peak in general popularity about 1912. On one occasion about that time, an overflow crowd at Orchestra Hall in Chicago was said to have battered down the doors to get in and hear a lecture on nutrition by Fletcher. Fletcher, like Metchnikoff, nevertheless died much sooner than expected — in 1916, when 66 years old and while trying to teach the Belgians how to live on their limited food supply (during the first part of the first World War). Popular interest in fletcherism waned rapidly after that and fletcherism became more or less replaced by a faith in expected nutritional miracles from the newly discovered vitamins.

I first learned of fletcherism when I was finishing my last year in high school in 1908. During the first few months of that year my general health declined. I found it increasingly difficult to study and dropped previously carried elective subjects in order to be able to devote more time to the required studies, especially mathematics (trigonometry). My appetite became very poor. Practically all foods seemed to ferment or putrefy more or less and gave rise to

flatulence. I regarded this as indigestion and a search for an explanation of indigestion and a remedy led me to read Fletcher's "A. B.-Z." (1). Fletcher maintained that indigestion was mainly due to eating without a normal appetite and that the first step toward remedying indigestion was to wait for the return of a normal appetite. The spring school vacation of one week was then at hand and I decided to try waiting during this vacation for a normal appetite to develop before eating. My intention was to wait (fast) during the entire week if necessary but my physical condition was already poor and I felt extremely weak after skipping a single meal. There was no evidence that a normal appetite such as Fletcher described (watering of the mouth for some particular simple food) was beginning to develop after a second meal was skipped. Hence, I abandoned the idea of fasting before the end of the first day. However, I ate practically nothing but small amounts of fruit during five days. I carefully masticated the food and gave its taste close attention, as suggested by Fletcher. I did not become weaker after the first day but I failed to regain strength and there was no evidence that a normal appetite was beginning to develop even after the fifth day. I feared that I would be too weak to do the necessary pre-graduation school work if I continued keeping my food intake restricted. Hence, I gradually resumed eating unrestricted amounts of my previous food. The regular food at first appealed less to my taste than before the five days of food restriction but it evidently was appreciated more after a few days.

On the first day of school following the spring vacation, I seemed to have recovered from the extreme weakness produced by my attempted fasting or semi-starvation but there was no evidence of having derived any benefit. However, on the next day, I felt a surge of physical exuberance and mental elation such as I had never experienced during the preceding five years. Instead of needing all of my

energy to concentrate on the school work in class and being otherwise quiet and reserved, I was able to follow the lessons with ease and had enough energy left to spontaneously behave in a boisterous manner. A classmate who was evidently disturbed by my antics wanted to know what on earth had come over me. I found that I could do the usual homework in mathematics in less than half the time that it previously took me and there was none of the previous uncertainty about having done the work correctly. In short, I seemed to be able to think more clearly. I made perfect grades in "math" during the remainder of the school year (during two months and in the final examination) and thus did better, during this period, than the "class genius" who later became a mathematician listed in *American Men of Science*.

This personal experience of physical and mental improvement from attention to my nutrition naturally impressed me greatly. Before this, I already believed that mental ability was influenced by one's physical condition but the only way to improve one's physical fitness seemed to be to take plenty of exercise. Thus, I indulged in vigorous exercise, particularly during the first part of my last year in high school (in the fall of 1907), but there was little evidence of any physical (or mental) improvement. In fact, I finally injured myself in practicing jumping and the necessary sudden curtailment of my physical activity probably was a factor contributing to my physical breakdown at that time. However, I believe that the lack of an adequate diet, because of economic and other circumstances, was the main factor leading to my breakdown. In any case, my experience after the spring school vacation made it evident to me for the first time that both physical and mental efficiency could be strikingly influenced by nutrition. I was puzzled somewhat by the fact that the improvement became evident after food restriction was discontinued and not during the period of food restriction as expected from Fletcher's explanations. Thus I concluded that it was merely "delayed evidence" of improvement produced by the preceding food restriction. I was surprised to find that so much improvement could be obtained without even having kept my food intake restricted long enough to acquire a normal appetite and without my digestion having been normalized. There still was considerable food fermentation and flatulence and this I then believed explained a decline in my physical condition or a loss of the initial physical exuberance which became apparent again within two weeks. Nevertheless, I felt that I had found the way to acquire previously undreamed of physical and mental powers and that permanent benefit would be secured if I followed Fletcher's advice as closely as possible and long enough to restore a normal appetite. I therefore waited only for graduation from high school before I began restricting my food intake again.

The results of my subsequent prolonged food restriction, particularly protein restriction and some fasting while working, proved to be practically disastrous

before the end of 1908. In short, I developed more or less nutritional edema but did not recognize it as such at that time and did not realize that it was produced or aggravated by food restriction and particularly by protein starvation. I simply found evidence that although I appeared to be underweight (weight in light clothing 128 lbs. — height 5 ft. 4 in.) my weight consisted partly of "dead weight" which I assumed to be an accumulation of waste matter and the water in which it was dissolved. An exclusive fruit diet or fasting was found to reduce the "dead weight" rapidly while an increased intake of ordinary food (including little protein) always increased the assumed accumulation of waste matter and water. I thought that I failed to remedy the situation because I never kept my food intake restricted long enough or rigidly enough to get completely rid of the accumulation of "waste matter" and I became too weak to continue working when I carried food restriction to extremes. Later, I found that I felt stronger when I ate unrestricted amounts of ordinary food but I did not seem to get rid of the accumulated "waste matter." Instead, the simple edema appeared to become a "fixed edema," "oily dropsy" or a fatty degeneration. I became very sluggish mentally and thought that the "fixed edema" was myxedema. Improvement became more difficult after that because an accumulation of fat was involved. Thus, with the exception of a few brief periods in which I thought that I was finally making distinct progress, my condition remained decidedly unsatisfactory during over four years.

Before 1912, I never fasted more than three days at any time because fasting seemed to be very difficult but by that time I thought that I had tried everything worth trying but prolonged fasting and I decided to try this as a last resort. The object still was to get rid of the supposed accumulation of waste matter and restore a normal appetite such as Fletcher described. As a preliminary to a longer fast, I tried to fast 10 days (using only water) in the summer of 1912 but weakness led me stop after having fasted only eight days. After that, I worked at a sweet corn cannery to earn enough money to tide me over the proposed longer fast without having to worry about where the food was to come from after that. I was able to do hard work during longer hours than any other man at the cannery after the eight-day fast but I was exhausted after that and postponed the beginning of longer fast until January, 1913. Then I stopped fasting after the 26th day and without having acquired a normal appetite. My intention was to continue waiting for a normal appetite to develop by drinking only dilute, unsweetened lemonade but the lemonade produced a gastric distress which called for bland food to serve as a remedy. Thus the fast was completely broken and I thought it was another failure. However, a few days later I had an experience somewhat similar to the one that followed the spring school vacation about five years earlier. Besides a surge of physical exuberance and mental elation, I then found that my appetite came closer to serv-

ing as an instinctive guide in nutrition than ever before. My mental outlook on life became greatly improved. One of my greatest previous handicaps was shyness but for some time after this fast I enjoyed mixing with people. I had no previous social affiliations but joined three groups within a few weeks after the close of the fast. One object was to meet someone whom I might marry. I went to work as a milk wagon driver partly to work outdoors and get plenty of exercise. This work tired most men but I often went to a gymnasium for other exercise after work or practiced heavy weight lifting at home. After accumulating some funds, I wanted to begin medical studies at a night school that was then still in existence (Jenner Medical College). It was impossible to enroll when I applied but I bought a human skeleton and did more or less studying at home. It was the most serious mental work that I did in five years.

Nevertheless the benefits derived from the 26-day fast again were not lasting. A physical decline became evident within about six months and I did not feel that I should try to undertake medical studies while working as a milk wagon driver. About a year after the 26-day fast, I felt in distinct need of more fasting to restore the lost physical and mental efficiency again. However, the 26-day was a terrible ordeal after which I practically swore that I would never fast another day in my life unless I could find a way to make it easier. Thus, in 1914, I began the practice of using cotton fiber as a non-nutritive substitute for food (7). Actually, I bought a roll of cotton batting to try for this purpose shortly after the close of the 26-day fast but I did not feel any immediate need of more fasting and did not try very hard to swallow the fiber until a year later. My activities between 1914 and 1918 largely concerned attempts to develop a form of cellulose more suitable for dietetic use than cotton fiber and attempts to interest others in the idea of using purified cellulose. Military service (1918-1919) interrupted this work but it led me to try intermittent fasting as a substitute for prolonged fasting.

In short, while still in the army but expecting to be soon released from service, I decided to try to improve my general physical condition by fasting in order to be better fitted to begin the manufacture of dietetic cellulose flour after receiving my discharge. I had an attack of pleurisy during the "flu" epidemic and did not feel well after the chest pains again disappeared. Prolonged fasting was out of the question but I was certain that I could fast one or two days at a time without interfering with my duties and I thought that the improvement might be cumulative if the intervals between the fasts were made short enough. Thus, I fasted about one day in three at first and found that the benefits actually were cumulative. After I had fasted about 16 days, I fasted every other day and I thought that I could continue doing so indefinitely without feeling that it would be an ordeal. It nevertheless became evident before I stopped fasting that I was becoming more easily

fatigued. I stopped fasting when I received my discharge from the army after having fasted 39 days out of 93 but never more than two days at any time. During the intermittent fasting my appetite became more instinctively determinative of my apparent nutritional needs than after the 26-day fast in 1913. After about the 12th day of fasting, I seemed to acquire an improved ability to write and I then wrote the first two of my published items. After I resumed eating daily, I felt more energetic than after my 26-day fast but this time I was eating large amounts of meat while I tried to adhere as closely as possible to a vegetarian diet after the 26-day fast. I do not believe that I could have overcome the difficulties that I met in beginning the manufacture of dietetic cellulose flour (Cellu Flour) without the energy obtained as a result or after-effect of the intermittent fasting.

Nevertheless, the improvement again was not permanent and I resorted to more or less food restriction or fasting from time to time after that. In 1922, I fasted 15 consecutive days and 15 days intermittently partly as a subject for Dr. Kunde's study of the after-effects of prolonged fasting on basal metabolism at the University of Chicago (8). Shortly after that I found that I could chin myself 25 times on a horizontal bar. That was the best chinning record I ever made. In 1923, I tried to duplicate, or improve upon, my intermittent fasting performance while in the army by fasting every other day and fasted altogether 53 days but derived no benefit. Instead, I developed more or less nutritional edema although I included as much protein (meat) as I wanted in the diet that was used on the days when I ate. I therefore thought that the diet included too much carbohydrate food and this led to a trial of a purely carnivorous diet with and without intermittent fasting. The results nevertheless were unsatisfactory. In 1925, I fasted 33 consecutive days, primarily for a study of the psychological effects of fasting by Glaze (9) but partly for my own study of hunger and appetite (10, 11). Glaze's study showed that mental performance was improved after fasting but the results in my case did not seem to be anywhere nearly as good as after the 26-day fast in 1913 or after the intermittent fasting in 1919. One possible explanation is that I ate as much food as I could eat after the 33-day fast to determine whether one could recover fully within an equal length of time. I began a 41-day fast on the 34th day after the 33-day fast. One object was to obtain further physical and mental benefit but the other was to use a diet restricted in protein after the second fast to determine its effect on the gastric secretion. I knew that such a diet might produce nutritional edema but I thought that I could prevent edema by simultaneously restricting the salt intake. However, the vegetables which I included in my diet evidently contained enough salts to promote the development of serious edema after such prolonged fasting and I failed to derive any benefit or was even harmed somewhat. In 1927, I therefore decided to begin a more conservative and systematic study of fasting and the type of diet to use. Thus,

I aimed to determine first how to obtain the most benefit from fasting one day at a time and I first tried fasting every other day with the use of different diets during different periods on the days when I ate. After five months of fasting every other day, I merely reached the conclusion that fasting every other day was too much fasting regardless of the type of diet used on the days of eating. Then I tried fasting one day in three for about three months. This proved to be of some benefit, especially when a relatively high fat diet was used which seemed to reduce hydration to a minimum. As a result, I stopped fasting because I felt well enough to do without fasting by simply using the relatively high fat diet. My belief now is that I felt much better than usual partly because I was experiencing the after-effect of the eight months of intermittent fasting but by 1928 my attention also became partly diverted to making studies on animals, mainly rats, at the University of Chicago. It is of course easier to observe the effect of fasting or a special diet on 100 or 1,000 rats than on oneself but some effects can not be understood without self-experimentation.

I already had an experience in the summer of 1908 indicating the striking influence that nutritional edema or excessive hydration could have on physical efficiency. At that time, I tested my endurance daily by chinning myself on a small trapeze rigged up for that purpose in my home. At the beginning of summer I was able to chin myself only six to eight times. I attributed an improvement to ten times to practice but I was surprised to find that I could chin myself 12 times on a hot Sunday morning in August although I felt weak. The weakness however was felt mainly in the legs. As I was then working six days in the week among chemicals in the basement of a laboratory supply house, I tried to get as much fresh air and sunshine as possible outside of working hours. Hence, I decided to walk about two miles on the sunny side of streets on the morning of the hot Sunday which incidentally turned out to be the hottest day in the year. I thought that a walk of more than two miles would tire me too much to do some reading later. However, after having walked two miles and having perspired freely in the meantime, I felt better than when I started and therefore decided to walk further. Thus, I walked 25 miles that day and perspired profusely during most of the time. Some of the muscles of my legs became sore before the end of the walking but otherwise I felt better than when I started. A chinning test after the walk showed that my endurance had increased in spite of some feeling of fatigue. I was able to chin myself 15 times and, after a night's rest, I was able to chin myself 22 times! The best record I ever made before that and after strenuous practice was to chin myself 19 times (in the annual test in high school in the fall of 1907). I lost at least six lbs. of "dead weight" as a result of the profuse sweating. The loss undoubtedly was due to a reduction in nutritional edema or a loss of excess salt and water although I then thought that it was due to getting rid of accumulated waste matter and

the water in which the waste matter was dissolved.

In 1908, I concluded that food (mostly "rabbit food") which needed the addition of salt to make it palatable should not be eaten because it fermented easily and contributed to the accumulation of "waste matter" but I did not blame the added salt. In fact, I developed a craving for salt later and licked salt to satisfy this craving. The importance of salt in the development of nutritional edema was not recognized until after my first 15-day fast at the University of Chicago in 1917 (12). After that fast, I gained two pounds daily during six consecutive days by ingesting nothing but water and cotton fiber which was flavored with lemon juice and salt. The first effect of a retention of salt and water after fasting is to make one feel better. In short, the retained salt and water evidently serves like a transfusion of a saline solution to counteract the dehydration produced by fasting but more than enough to increase weight a few pounds becomes so much "dead weight" or nutritional edema and produces physical and mental sluggishness. Further tests in 1917 showed that my weight after the 15-day fast was increased as much as 12 lbs. in one day by a diet including salty ham and cabbage.

The value of a liberal protein intake to prevent, minimize or reduce nutritional edema first became evident to me in connection with my intermittent fasting in 1919 but the value of a high fat or low carbohydrate diet was not observed until 1927. A diet high in fat and protein or low in carbohydrate seemed to prevent the development of colds (13) but it tended to decrease physical and mental efficiency in the long run, apparently by producing excessive dehydration. Thus, in 1933, a loss of private funds by "experimenting" in the stock market made it necessary to do work involving considerable physical strain and a diet relatively high in carbohydrate seemed to be best for this purpose. More or less edema nevertheless developed and some fattening also occurred. This next led me to try a diet relatively high in protein and low in total calories. The improvement produced was striking. After being about two weeks on this diet, I felt much more energetic, more mentally alert and freer from shyness for a time than ever before. In fact, I became almost too "nervy" for my best interests during a short period. The diet which I used was somewhat similar to the "anti-retention" diet advocated by Földes (14) but in prolonged use I found that the amount of food I ate was not sufficient for maintenance. That is, the diet served to reduce edema and fat (15) at first but increased the susceptibility to the development of edema from undernutrition again in prolonged use. It is easy to understand from such an experience how opposite conclusions concerning the value of a specific dietary regimen can be reached.

As a result of the foregoing experience, I largely avoided nutritional extremes between 1936 and 1940 and gave attention mainly to the influence of mechanical laxatives on physical well-being and mental clarity.

Thus, I found that a mixture of ground, purified kapoc and psyllium seed husks at first seemed to serve as well as intermittent fasting under favorable conditions but in the long run the initial improvement was not maintained. Alvarez at one time suggested that the best way to use a cellulosic laxative might be to use it only about twice weekly. I never tried that but it may be that a periodic variation in the non-nutritive fraction of the diet would be of some value.

In 1941, I began trying periodic short fasts again. The object was to determine whether improvement such as I noted during the first part of my intermittent fasting in 1919 might not again be secured by particularly avoiding fasting too much. First I tried fasting two consecutive days each week with the use of a diet designed to keep hydration at a minimum between fasting but this seemed to be too much fasting to be practical at the age which I had attained. Hence, I tried fasting only one day each week and used the same diet. This appeared to be of no value but observations made on my gastric secretion suggested that the diet which I used kept hydration too low or slowed down normal rehydration after the fasting. An increase in the proportion of carbohydrate in the diet, particularly immediately after the fasting days, remedied this (16) but no cumulative benefit from fasting one day per week was obtained. Perhaps fasting one day in six or five or three successive days every other week would be of more value but I have become conservative with age and have simply continued fasting one day per week during over six years. Only minor modifications of the diet have been tried. Obviously, at my present age (59), I can not easily do what I could do at about half this age and the same nutritional regimen can not be expected to yield the same results. Fasting one day per week produces a weekly variation in the feeling of well-being and general efficiency or the rate of aging which I at least prefer to the monotony of aging regularly or steadily (some say gracefully) by eating moderate amounts of food regularly.

In any case, after 40 years of almost continuous personal nutritional experimentation including over 900 days of fasting, I believe that the most worthwhile peaks of physical and mental efficiency are attainable as after-effects of more or less fasting or food restriction before the age of 40. Naturally, fasting or dieting after growth has been practically completed can not serve as a substitute for a superior (inherited and acquired) constitution. The greatest physical and mental efficiency attainable as an after-effect of fasting or food restriction may never be greater than that attainable early in life with a satisfactory and regularly used diet. Thus, I stated that after the spring school vacation in 1908 during which I restricted my food intake "I felt a surge of physical exuberance and mental elation such as I had never experienced during the preceding five years" but I felt that way five years earlier. At that time I lived

away from home during a year (1902-1903 — age, 13-14) and had a much better diet than during the preceding five years and subsequent five years. My mental ability was unquestionably better while I was on the better diet than it was before or afterward but my deportment was inferior because I had enough "spunk" and energy to make life miserable for my teachers. My physical and mental efficiency apparently never became greater later but it was approximated under the best conditions and made me feel as if I had been rejuvenated. The state of nutrition, metabolism or physiologic functioning attainable during at least short periods after fasting or food restriction therefore creates a situation in which the enthusiasm, energy and basic ability of an earlier period of life is combined with more mature experience. In my opinion, the claims that the founders of most of the world's great religions began their public careers by fasting the traditional 40 days have factual bases which explain the results. The fact that many individuals manifest great physical and mental ability without ever fasting or restricting their food intake does not rule out the likelihood that they would do much better during some periods if they fasted or restricted their food intake occasionally. It has occurred to me that periodic intense activity may also have an effect on metabolism similar to periodic food restriction.

Fletcher, Kellogg and Fisher supported the view that a vegetarian or meat-less diet or one containing a minimum of meat served best to promote physical endurance. Tests made with a finger-ergograph before I began my first 15-day fast at the University of Chicago in 1917 revealed that I had unusual endurance (12). I was then living on a meat-less diet but I did not feel strong — I lacked pep. Nevertheless I always felt that I could continue pulling up the weight used in the ergograph tests until I would faint from the strain or from the muscular pain that developed after a few minutes. It was therefore agreed that I should stop each day after a 30-minute test. It was obvious to me after the first test that the apparent unusual endurance was due to bringing endocrines (presumably the adrenals) into play after some pain was experienced. A much larger and stronger subject was unable to raise the same weight more than about five minutes but my impression was that he stopped trying when pain developed. On one occasion he was however induced to keep on trying to raise the weight (in unison to the beat of a metronome) after he apparently could no longer move it. His facial expression indicated that he experienced considerable pain and he evidently became angry because he was accused of not trying hard enough and was being satanically urged to keep right on trying. After a few minutes he again began raising the weight but by that time it became obvious that he was too angry to make it wise to prod him much further. Presumably his adrenals supplied the needed energy to raise the weight again or he attained his "second wind." A vegetarian or low protein diet or fasting may therefore increase endurance by promoting a

hypertrophy of the adrenals which makes it easier to bring them into play and thus tap those commonly unused human resources or reserves which William James stressed.

Finally, what about the main tenets of fletcherism? I believe that Fletcher's first principle — wait for a normal appetite — was sound but Fletcher's concept of the nature of a normal appetite (meaning hunger and appetite) was erroneous or applicable only to certain conditions. However, the most widely accepted authorities simply seem to have made a greater confusion of the explanation of hunger and appetite since Fletcher's time. Fletcher evidently came closer to the truth because he did more personal experimenting. He reduced his weight considerably to begin with and fasted at least 16 days on one occasion (against Dr. Kellogg's advice). The superficial followers of Fletcher largely ignored his first principle and placed the main emphasis on chewing like cattle. Fletcher, like I at first, failed to distinguish between the direct effects of food restriction and the after-effects and effects under differing conditions. My guess is that Fletcher practically killed himself by practicing what he preached. As is now well known, a

restricted low protein diet such as he regarded as most satisfactory would promote the development of nutritional edema and Fletcher probably died of pneumonia because of this. Perhaps we still do not know how to restrict the food intake or fast wisely but that does not justify the still too common neglect of nutrition, especially the failure of educators to realize that no one can be taught to think — that thinking is a spontaneous physiologic function of the normal brain which is influenced considerably by nutrition.

SUMMARY

The high-lights are presented of 40 years of personal experimentation in which the chief aim was to improve or maintain physical and mental efficiency by nutritional means. This experience involved over 900 days of fasting and the trial of various diets. As a result, it is concluded that the most worth-while peaks of physical and mental efficiency are attainable as after-effects of more or less fasting or food restriction before the age of about 40 years. The complication of food restriction by nutritional edema is incidentally discussed.

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Nutrition Notes

Your Health and the Soil

E. P. McKinney, M.D. (1) of Texas, at the State Medical Association and before the Section on Public Health at Dallas in May 1947, read a valuable paper dealing with the vital importance of maintaining soil fertility if we are to maintain human health. "Studies in ecology and nutrition have repeatedly shown the close relationships between the fertility of the soil and the health of the peoples subsisting on foods produced from such soil." He feels that the utilization of artificial vitamins and accessory food factors in the medical treatment of vague, undiagnosable nutritional conditions is unsatisfactory and wasteful and

that the true basic approach is through improvement of soil fertility and its corollary, soil conservation. Food plants grown in a deficient top soil will produce poor feeding results. "The thieving trinity of wind, water and man's neglect have robbed us of untold millions of tons of fertile topsoil." He advises medical men in general to learn more about the soil by talking to the county agricultural agents because he realizes that actually, agriculture has almost become a medical problem. He feels that methods of enriching the soil constitute the *basic approach* to the health of our people and to the preservation of our culture, and that without such a program, we are a doomed people.

These words are probably not too strong. Dr. M.

L. Fuller, in discussing Dr. McKinney's paper, referred to the work of Howard in England and to G. I. Wrench's remarkable book regarding the Hunza nation. There is evidence that the medical profession is becoming increasingly conscious of the unspeakable need for an improved agriculture in this country. It is probably from the medical profession that the seeds of this tremendous reform will spring.

Behind the Menu

In Canada the habit of eating in restaurants has increased greatly in the past two years and the Department of National Health and Welfare has produced, through the facilities of the National Film Board, a movie which deals interestingly and in detail with the whole subject of restaurant hygiene. This film was previewed by the Canadian Restaurant Association and points out the need for planned layout of kitchens and dining rooms as well as staff washrooms and locker rooms, and urges correct handling of food and utensils. The point is stressed that public health cannot be guarded by laws and regulations alone, as these must be backed up by the understanding and cooperation of the restaurant industry. *Behind the Menu* recognizes the importance of avoiding crowding, the provision of adequate refrigeration, and care in dish washing. Chipped and cracked dishes are discarded as they cannot be cleansed of bacteria. Pests are controlled by insect sprays and powders. Every year food-borne diseases render thousands of persons ill. Some of the diseases may be served up at ten dollars a plate and others are hidden in a ten cent sandwich. In the taverns and dining rooms in Canada are displayed signs stating the number of customers who may be seated, it being contrary to law to exceed this number.

Nutrition and Resistance to Infection

While it is assumed that mass starvation favors epidemics of infectious disease, it is difficult to prove, because famine is only one of a number of serious dislocations which usually include breakdown of san-

itary precautions and general demoralization. Superficial skin infections are unduly common during starvation owing to lowered resistance of the skin. Probably anti-body production is adversely affected by starvation because of the well-known lowering of serum protein. In a human experiment in Germany, undernourished individuals produced a lower response to antigen injections than normal persons (1) and it was felt that this comparative failure in anti-body production was due specifically to malnutrition. Nevertheless the difference between the controls and the patients was not great, and the fact that no great epidemics have occurred in Germany since the war, suggest that malnutrition may not be a very important factor in producing lowered resistance to infection. On the other hand, there is a high general mortality rate, and a high morbidity rate for tuberculosis in the malnourished, and famine produces an appalling, demoralizing effect which is a serious psychologic problem in itself.

The toxin sensitivity is known to be affected by the nutritional status of the host. For example, diphtheria toxin units with ascorbic acid, and a very high ascorbic acid intake may reduce the sensitivity of the host to diphtheria toxin. Probably the optimal ascorbic acid requirement is increased in all fevers (2).

Vitamin A deficiency causes an atrophy of the epithelial surfaces followed by keratinizing metaplasia and lowered local resistance. In patients who had recovered from rheumatic fever it was found that relapse occurred in those having low blood vitamin-A levels but not in those presenting a high vitamin-A level (3).

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Abstracts on Nutrition

TURNER, DOROTHEA F.: *Nutrition and dietetics.* (Nutr. Rev., October 1947, V. 5, No. 10.

NELSON, W. E.: *Treatment of diabetes mellitus in children.* (Texas State J. Med., March 1948, V. XLIII, No. 11, 677-681).

Nutrition is the combination of processes by which the living organism receives and utilizes the materials necessary for the maintenance of its functions and growth and renewal of its components. *Dietetics* is the combined science and art of feeding individuals or groups under different economic and health conditions according to the principles of nutrition and management. The acceptability of foods to the patient is now being recognized as the largest single factor in effecting a change in food habits.

In the treatment of coma the author continues to use infusions of sodium bicarbonate as indicated since certain animal experiments showed better recovery when alkali was used. He also uses glucose in addition to insulin. In the management of non-acidotic cases he employs rapidly absorbed types of insulin in patients under five years of age, using both these and those of delayed absorption in older patients. He has considerable to say with respect to the psychological aspects of treating juvenile diabetics.

CLINICAL RECORD

NUMBER

Date

Name

Address

Chief Complaint

Present Illness

Past Illness

Family History

Physician

foster recovery with

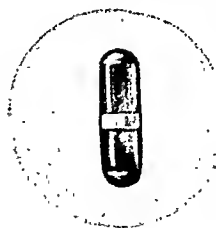
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RICE, C. O., STRICKLER, J. H., ORR, B., AND SANDERSON, D.: Parenteral nutrition (pre- and post-operative use of glucose, amino acids and alcohol — a preliminary study). (Jour. Lancet, March 1948, V. LXVIII, No. 3, 91-95).

In order to supply caloric needs, as well as vitamins, via the intravenous route before and after operation in ill-nourished patients incapable of receiving food orally, the authors have devised a mixture of amino-acids, glucose, vitamins and alcohol, the latter not only supplying calories but affording

such excellent post-operative sedation and tonic effects on bowel and bladder that morphine is unnecessary. Above all the method eliminates the weakness and post-operative illness and facilitates early ambulation. Since fat cannot as yet well be given intravenously, alcohol supplies the calories thus missed. The formula is as follows: vit. B complex and vit. C, fluids 3000 cc.; sod. chloride 6-18 grams; glucose 150 to 180 grams, amino-acids 100-150 grams; alcohol (95 per cent) 120-180 cc. Total calories 2020 to 2400. Directions for the speeds of injection are given and should be consulted. The technique has been used in more than 300 operative cases without ill effects.

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*Peete, D. C.: Nutrition in Cardio-Vascular Disease, Geriatrics 2:213 (July-Aug.) 1947.

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STRANSKY, E. AND PECACHE, L. V.: *Hand-Schuller-Christian's Disease (xanthomatosis or cholesterol storage disease)*. (Acta Med. Philippina, Oct.-Dec. 1947, V. IV, No. 2).

The authors report the first case of the title disease to be seen in the Philippines, a peculiar syndrome, characterized by partial destruction of the bony structures of the skull, storage of cholesterol at first in the marrow of the flat bones and later in the long bones, diabetes insipidus, due to storage of cholesterol near or in the posterior lobe of the pituitary gland and finally by exophthalmus, due to cholesterol deposits in the retrobulbar space. While the disease is definitely a storage disease, it is probable that in cases where the cholesterol level of the blood serum is normal, it is not a constitutional disorder but rather a secondary storage disease due to a primary reticuloendotheliosis.

LEDERER, J.: *The treatment of diabetes by a high-carbohydrate, low-fat diet*. (Acta G. E. Belgica, January 1948, V. XI, No. 1, 7-22).

The substitution of a high-starch, moderate-fat diet for one high in fat and low in carbohydrate in 11 cases, permitted a smaller insulin dose in eight, required the same insulin dose in two, and a higher insulin dose in one case, and in all cases the general condition was considerably improved.

CHUTE, A. L.: *Survey of patients with juvenile diabetes mellitus*. (Am. J. Dis. Child., Jan. 1948, V. 75, No. 1, 1-10).

This is a review of 123 cases of diabetes in children (whose ages at onset varied from less than one year to 14 years of age), the disease developing prior to 1932. Fifty-two are living, 58 are dead and 13 could not be traced. Twenty-nine patients survived for 20 years and 24 still are living. Those surviving showed pronounced evidence of degenerative lesions, particularly arteriosclerosis, albuminuria, and retinitis. Is insulin, then, the complete answer to diabetes or are there undiscovered causes for the vascular complications? Can stricter control by diet and insulin be the answer? Until we learn more, probably this is our best bet, and we ought not to follow the example of those who advocate free diets with insulin sufficient only to prevent ketosis and symptoms, without any attempt to keep the blood sugar within normal limits.

DRAPER, A. J.: *Rational treatment of diabetic acidosis*. (Southern Med. & Surg., Dec. 1947, V. CIX, No. 12, 397-400).

Ketosis (increased beta-oxybutyric acid, diacetic

acid and acetone in the blood) actually represents an attempt at a *fuel supply* in the absence of glycogen, since these bodies are oxidized normally by a diabetic. The glycogen lack is due to insulin failure. Infection abets it. The acid bodies call out sodium ions to neutralize them preparatory to excretion and consequently there is a loss of sodium ions and with it extracellular and intracellular fluids. Renal functional impairment results from loss of fixed base and hemoconcentration and gives rise to acidosis (shift in pH of blood to the acid side). The needs of the patient in diabetic acidosis are insulin, water, salt and possibly plasma of whole blood. In some cases a potassium deficiency develops and requires administration of potassium iodide. The old argument persists as to whether or not to use glucose, but the author favors it. He disbelieves in the advisability of enema and gastric lavage, as they become unnecessary when salt balance is restored.

GILMORE, C. M.: *Muscle atrophy from sensitivity to protamine zinc insulin*. (Southern Med. & Surg., Dec. 1947, V. CIX, No. 12, 394-395).

Three cases are presented exhibiting some atrophy in the left thigh, the region used for injection of insulin. No clue as to mechanism is given. It is suggested that the injections be spread over different portions of the body.

SCHNEIDER, R. W. AND KAMMER, H.: *Hyperparavitaminosis D (report of nine cases)*. (Cleveland Clinic Quart., V. 15, No. 2, 82-89).

The symptoms of overdosage with vitamin D resemble those of hyperparathyroidism and consist of polydipsia, polyuria, muscular weakness and headache and less frequently, drowsiness, nausea, vomiting and diarrhea. Hypercalcemia is attributable to a rise in the ionizable calcium fraction. Toxic symptoms may result in persons taking vitamin D in whom elevated blood calcium levels cannot be demonstrated. Vitamin D may be a primary irritant to tissue cells in some individuals. Chief harm attending excessive administration of vitamin D is derived from metastatic calcification, and renal damage of a severe grade may result. In all nine cases reported, significant impairment of renal function was present. Discontinuance of vitamin D resulted in disappearance of toxic symptoms in all cases and kidney function improved significantly in the seven cases followed up. In the two cases in which metastatic calcification outside the kidney was present there was no evidence of roentgenologic improvement during the period of observation. Most of the cases had been taking the vitamin for arthritis, some for much longer periods than others.

Editorial

NUTRITIONAL EXPERIMENTS ON ONE'S SELF

WHAT CAN BE LEARNED by conducting more or less systematic feeding experiments upon one's self? Obviously the results will consist in both physical and mental reactions, especially where drastic measures are employed, and the individual will learn at first hand "what it is like" to fast, starve, or even glutonize. He will also learn what dietetic measures seem to possess virtue and also what measures appear to result in harmful effects. His work, even when carefully recorded, will lack the value of repetition, upon which in animal and clinical experiments, we have come to place so much reliance. Nevertheless, his record will possess one very great value — it will indicate the psychological inspirations to experimentation, and the mental effects of such painstaking and not infrequently hazardous trials. It will indicate how *this* man reacted to *this* kind of deprivation or excess.

Frederick Hoelzel, well-known in physiological circles, describes elsewhere in this issue, his reactions

to fletcherism, which now enjoys merely an historic interest, also his periods of extreme mental clarity following short periods of fasting, and his development of nutritional edema while following a very low protein diet. Starvation did not cause him to acquire a normal appetite, probably because of induced atony of the gastric musculature. He later sought artificial means of combatting hunger pains. There is a whole literature dealing with the effects of fasting on the mind and spirit of man. Many religious geniuses have employed the method. Hoelzel's genius is physiology and he persisted, until quite recently, in various modifications of fasting.

A full nutritious diet passes as good coin today, and Hoelzel shows us for a moment the obverse of the coin. His 40 years of nutritional experimentation upon himself may indeed be unique, especially by a physiologist, and for that reason his article possesses unusual interest.

Book Review

ADVANCES IN PEDIATRICS, VOLUME 3. Pp. 363, (\$7.50), Interscience Publishers, New York, 1948.

This is not a systematic treatise on pediatrics but rather a group of original essays on subjects of great current importance, each written by an authority in his own field. It is an extremely interesting book. The subjects dealt with are as follows: *Effects of birth processes and obstetrical procedures upon the newborn infant* (Clement A. Smith); *Retrolental fibroplasia* (T. L. Terry); *Emotions and symptoms in pediatric practice* (Milton J. E. Senn); *Therapeutic agents in the treatment of epileptiform seizures* (William G. Lennox); *Viral hepatitis* (Joseph Stokes, Jr.); *Abnormalities and variations of sexual development during childhood and adolescence* (Lawson Wilkins); *Puberty and adolescence: psychological considerations* (Hilde Bruch); and *The osteochondroses* (Beckett Howorth). After reading these essays one

gains the impression that, in this volume, very accurate and well-seasoned judgments have focused definitely clearer light on the subjects treated than could be obtained from conventional works on pediatrics. The psychological aspects of childhood diseases here receive due consideration, but there is a well-tempered restraint in assigning to the mental sphere no more than it deserves. None of the essays in which the psychological aspects are important, can be said to over-rate the same, but in each case an obvious critical judgment and selection has been made. Retrolental fibroplasia will prove of specific interest to every practitioner. Lennox's essay on epilepsy exemplifies the author's tremendous erudition, as focused on the pediatric problem. Senn's method of handling the emotional field in children is a contribution to general culture and biology as well as an invaluable guide in a specific field. The other essays are all likewise lessons in brevity, clarity and utility. The volume is enthusiastically recommended, not only to the pediatricist, but to every student of disease.

General Abstracts Of Current Literature

ABSTRACT EDITOR — M. H. F. FRIEDMAN

Jefferson Medical College

1025 Walnut Street

Philadelphia, Pennsylvania

CLINICAL MEDICINE

MOUTH AND ESOPHAGUS

SCHMIDT, H. W.: *Cicatricial stricture of the esophagus.* (Proc. Staff. Meet. Mayo Clinic, June 9, 1948, V. 23, No. 12, 265-267).

A symptomatic esophageal hiatal hernia ought not to remain untreated. Vomiting leads to esophagitis, due to acid gastric contents coming in contact with the mucosa of the esophagus and the end result is final contraction of scar tissue with stricture. Prolonged vomiting from any cause may have the same final results. In cases of ingestion of caustic liquids, continued close endoscopic observation for at least three months is necessary since scar tissue does not at once form, and early X-ray studies may be as negative as the symptomatology. Marked reduction in mortality rates in thoracic surgical procedures has broadened the indications for surgery of the esophagus. Intrathoracic and antethoracic esophagoplasty following excision of the cicatrized area of the esophagus are becoming more common. Usually much can be done by the endoscopist through dilatation and where dilatation is possible, results are better than following radical procedures.

BOLADERES, J. L.: *Reestablishment of esophago gastric continuity by means of a jejunal loop, following resection of the esophagus for cancer.* (Bol. de la Seccion de Sinidad de la Policia Nacional, Feb. and March 1948, V. IV, No. 13, 410-417).

Three cases of cancer of the esophagus are presented in which an esophago-gastrectomy was done since technical difficulties made it impossible to do a direct esophago-gastrostomy. In these three cases esophago-jejunosomy was performed and in one case a free loop of jejunum was mobilized and brought up into the thorax, filling the gap between the esophagus and stomach.

STOMACH

PUTNEY, F. J.: *Thoracic stomach produced by esophageal hiatus hernia and congenital short esophagus.* (Ann. Int. Med. June 1948, V. 28, No. 6, 1094-1105).

Thoracic stomach results from herniation through a normal or abnormal diaphragmatic opening, or failure of development of the esophagus. In most instances the stomach gains access to the thoracic cage through the esophageal opening in the diaphragm. The symptoms are variable and may simulate those of gastro-intestinal, cardiac, respiratory or gall-bladder disease. The commonest symptom is dysphagia, but there may be no symptoms at all. Diagnosis is by esophagoscopy or X-ray. Esophagoscopy also has a place in therapy, for relief may be obtained for varying periods of time by topical application to an ulcerated area and dilatation of an existing stenosis. Surgery should be deferred as long as the patient is tolerably comfortable.

BRYNJULFSEN, CHR.: *Twenty years of treatment for gastric cancer,* (Nordisk Med., July 23, 1948, 1402-1405).

In 260 operative cases of cancer of the stomach during the past 20 years, gastric resection was done on 131, gastro-enterostomy on 58 and exploration on 71 cases. In the resection group, 29 per cent were alive after three years, 17.3 per cent after five years and 10.4 per cent after ten years. Radical resections are better than palliative resections, so far as survival is concerned — five times as many survived five years. Nevertheless, palliative procedures are valuable, giving an average survival of 19.4 months. A case must survive ten years to be considered cured. The author concludes that really good results cannot be achieved in gastric cancer by the present diagnostic and therapeutic means at our disposal.

FORSGREN, E.: *Gastric function tests.* (Nordisk Med., Feb. 7, 1948, V. 39, No. 27, 1289-1292).

The author believes it is of value to include gastric analysis as a routine part of an examination, even when no disease of the stomach is suspected, partly to assess the physiology of the patient and discover what effects psychological disturbances may have on gastric secretion. He thinks repeated gastric analyses ought to be made at different times in the day. The Ewald meal is suitable in the morning but a meal ought to be used in the evening. He adds sharp-cornered cubes of boiled egg-white to help him judge the degree of digestion.

COOPER, R. R.: *Gastrosopic study of radiologically negative dyspepsias*. (Harper Hosp. Bull., May-June 1948, V. 6, No. 3, 74-78).

There is a large group of radiologically negative dyspepsias which can be shown to have mucosal changes by gastroscopy. Existence of organic gastric disease by X-ray alone was 26 per cent, by gastroscopy alone 54 per cent and, by both methods, 66 per cent, in a series of 230 gastroscopies on 175 patients.

KINSELLA, V. J.: *Diagnosis of gastric disease — should radiology of the stomach be abandoned?* (Med. J. Australia, May 15, 1948, V. 35, No. 20, 610-614).

The essence of this article is that a negative X-ray report on a stomach, in the presence of symptoms suggesting gastric disease, should lead either to immediate exploratory laparotomy or repetition of the X-ray examination at an early date. The article represents a kind of rebellion by a clinician against the inherent errors of radiology.

COLCHER, H.: *Gastroscopy with transparent balloon. Method for the visualization of the "blind areas."* (Am. J. Med., V. 3, p. 423, Oct. 1947).

A transparent balloon is attached to the lower end of the flexible gastroscope. This is used for distension of the stomach. The lesser curvature becomes straightened when the balloon is inflated and thus makes visible an area usually "blind."

BOWEL

KELBY, G. M.: *Submucous lipomas of the ileocecal valve*. (Journal-Lancet, Aug. 1948, V. 68, No. 8, 301-304).

Submucous lipomas of the ileocecal valve are rare and the author describes two cases. Abnormal roentgen appearances were obtained suggesting malignancy. One case had symptoms referable to the tumor while the other did not. When symptoms are present, they are probably caused by intussusception, obstruction or both.

NASLUND, A. W.: *Conditions simulating the roentgen appearance of intestinal obstruction*. (Journal-Lancet, Aug. 1948, V. 68, No. 8, 312-313).

The author makes the statement that when a scout film of the abdomen shows unmistakable and marked distention of both the small and large bowel, that paralytic ileus is present. Spastic ileus cannot always be differentiated from mechanical obstruction. Indeed,

differentiation between mechanical obstruction and a paralytic or spastic ileus is usually impossible by means of X-ray alone.

KLORSTOCK, A.: *Amebiasis in Palestine*. (Hebrew Medical Journal, 1948, V. 1, 176-171).

Infestation with amebae is high in Palestine and the chronic form accounts for a large amount of the disability seen. The acute form is rather mild in Palestine. The author attempts to give due credit to *Entamoeba histolytica* for illness in persons harboring the organism, while making just allowances for the effects of nervous indigestion. Constipation and low gastric acidity are common and he thinks that amebic appendicitis is an actual entity. Acute amebic hepatitis is not rare, but true amebic abscess of the liver is rarely seen, as in other hot climates. Stool culture raises the number of positive diagnoses. He uses the culture medium of Adler and Foner (see Lancet 1.) which he says is not well-known but highly satisfactory. The complement-fixation reaction was 80 per cent reliable in diagnosis of cases proved positive by smear or culture, but it gives no clue as to whether the infestation is current or historic. The acute dysentery and the hepatitis respond well to emetin, but he feels that for the chronic forms, no quick reliable means of treatment exists. The disease is endemic and passed along by thousands of "carriers," and in Palestine the hygienic problem cannot at present be satisfactorily dealt with.

VIGONI, M.: *Modern contributions to the treatment of ulcerative colitis*. (Acta Gastro-Enter. Belgica, Nov.-Dec. 1947, V. X, No. 8-9, 519-529).

The author recently visited American clinics where he gained the impression that not only is the disease much more common in America than Belgium but that a higher degree of specialization in its study and treatment has taken place. He reviews practically every thing he saw in America, including chemotherapy, surgery and Bagen's vaccine and serum. He believes that liver extract is a valuable adjuvant in therapy. While the psychic state is not unrelated to the disease, he hesitates to regard the disease as psychogenic. He sees no relationship between the disease and bacillary dysentery. He regards colostomy as a well established mode of treatment.

FAILE, E. DEC.: *Pyloric spasm simulating congenital hypertrophic stenosis — report of a case*. (Lancet, No. 6508, p. 794, May 22, 1948).

An infant six weeks old had a history of vomiting for four weeks. The infrequent stools were soft and yellow. An operation revealed no abnormality of the stomach or intestine. Vomiting persisted after opera-

tion. A bismuth meal showed almost complete obstruction at the pylorus. The diagnosis of pyloric spasm was thus made and glyceryl-trinitrate given. The effect was immediate improvement; gain in weight was maintained. Eventually the pyloric spasm passed off and the pylorus became normal. Glyceryl trinitrate was also tried in patients with proved hypertrophic pyloric stenosis but without success.

HANSEN, P. B.: *Spontaneous chronic intestinal invagination in adults.* (Acta Radiol. V. 28, p. 115, 1947).

Diagnosis of intussusception, a condition rarer in adults than in children, is made by barium enema or by contrast enema with a barium meal. In the majority of cases the cause of intussusception in the adult is a tumor. A barium meal may show a prolonged traverse time of the barium, and dilatation of the terminal ileum with stricture at point of junction with the cecum. A barium enema will show a smooth end of the barium column, bicornate configuration, filling of the colon with a stripe-like effect and partial filling of the invagination sheath with stripes corresponding to the haustra, and gaseous distension of the terminal ileum. The hepatic flexure is depressed while the cecum is raised, and the colon involved shows dilatation.

METZ, A. R.: *Duodenal regurgitation.* (Arch. Surg., V. 55, p. 239, 1947).

This study is based on the histories of 15 patients. Metz considers duodenal regurgitation to be a clinical entity that has been neglected in study. The cause usually is pressure on the duodenum by the mesenteric attachment at the point where the intestine passes over the spine. Ptosis of the abdominal viscera is usually found in these patients. The degree of obstruction determines the severity of the symptoms: from nausea and weight loss to vomiting following a meal, exhaustion, dehydration, emaciation and death.

Fluoroscopy is an important diagnostic aid: the stomach is usually J-shaped with the cap placed high; the duodenum is greatly dilated, and the obstruction is noted to the right of the spine. The barium meal will be seen to regurgitate into the stomach, and then forced out again, perhaps past the obstructed region.

Bed rest, and frequent small feedings with alterations in body position are helpful. Advanced cases must be subjected to operative relief. Gastroenterostomy or duodenojejunostomy, as determined by the condition, are the operations of choice.

COLON

DEVINE, H. AND DEVINE, J.: *Subtotal colectomy and colectomy in ulcerative colitis.* (Brit. Med. J., July 17, 1948, 127-131).

The authors, as the result of favorable experience

in the use of partial or complete colectomy in 11 very severe cases of chronic ulcerative colitis, advocate the operation at as early a date as it can be ascertained that medical treatment will not cure. Only two of the 11 cases died, while six recovered and appear to be cured, one after six years. They describe a "gradual" method for colectomy in which the colon is placed out of function for several months prior to its removal.

PANCREAS

BAKER, J. W. AND DURHAM, M. W.: *Associated pancreatic necrosis and biliary disease.* (Surgery, Feb. 1948, V. 23, No. 2, 301-305).

On operating on a woman for known cholecystitis with stones, pancreatitis with fat necrosis also was found. Cholecystostomy with removal of gallbladder stones was done and catheter drainage of gallbladder instituted. Cholangiograms later revealed multiple stones in the common duct which were passed following irrigation with 1:500 nupercaine solution in normal saline. The pancreatitis subsided and patient made a good recovery. The relaxation of the Sphincter of Oddi by nupercaine obviated the necessity for further radical surgery. Pancreatitis is often best treated, and with a lower mortality rate, by conservative methods. Probably serum amylase estimations should always be done, prior to operation, in acute inflammations of the upper abdomen.

BICKFORD, B. J.: *Traumatic pseudo-cyst of the pancreas with pleural effusion.* (Brit. Med. J., June 12, 1948, 1134-5).

Two cases of pseudocysts of the pancreas are described. These "pseudocysts" are due to the escape of pancreatic secretion into the tissues after injury or acute pancreatic necrosis or in association with chronic relapsing pancreatitis. The most satisfactory operative procedure is primary anastomosis of the cyst to the stomach or jejunum where possible. In these two cases the associated pleural effusion was not explainable.

PAVEL, I.: *Investigations on the etiology of diabetes. The clinical pancreatitis.* (Bull. Acad. Med. Roumania., V. 14, p. 629, 1943).

Pancreatitis probably occurs more frequently than is observed or reported. From various sources the incidence of pancreatitis following mumps has been placed as high as fifty per cent of the cases. Hyperglycemia and diabetes may develop after mumps. In other infections pancreatic injury with pancreatitis and diabetes are also common. Included are pneumonia and catarrhal jaundice in which the damage to the pancreas is reversible.

ULCER

HARALDSON, S.: *Prognosis in conservative treatment of bleeding peptic ulcer.* (Nordisk Med., April 16, 1948, V. 38, No. 16, 778-783).

Out of 1075 cases of peptic ulcer treated over a ten year period in Helsingborg Hospital, Sweden, 218 (or 20.3 per cent) had massive hemorrhage and 13 of the cases died, a mortality of six per cent among those with profuse bleeding. In four of the cases ending fatally, complicating diseases were present and it is uncertain whether death could be attributed solely to hemorrhage in these instances. Long continued follow-ups for 10 years showed that results actually were *not* good, as 54 cases had one or more recurrent hemorrhages, three ending fatally: there were three cases of perforation, one of which was fatal: 15 patients died of cancer of the digestive tract: 25 patients eventually came to surgery for ulcer: and only 35 cases had no trouble at all. Prognosis is worst in patients over 40 years of age, and therefore all cases over 40, who have severe hemorrhage should be transfused and subjected to operation without delay.

SURGERY

SMITHWICK, R. H.: *Total gastrectomy.* (New England J. Med., V. 39, p. 237, 1947).

Operative mortality in total gastrectomy has decreased greatly during recent years. This is due to better pre- and post-operative care of the patient and to increased experience. The operation has more to offer for survival in gastric cancer than less radical procedures and perhaps should be used more often.

The closed esophagojejunostomy procedure is used by Smithwick. This is "aseptic" and lessens the mortality from local contamination and peritonitis. The case histories of two patients surviving total gastrectomy more than five and ten years respectively are given.

EXPERIMENTAL MEDICINE

PHYSIOLOGY

MATTIL, K. F.: *Digestibility of fats: a correlation of experimental data.* (Oil and Soap, V. 23, p. 344, 1946).

The digestibility coefficients of various fats as obtained in experiments presented in the published literature were analyzed statistically. The higher the content of saturated fatty acids in the fat the lower was the digestibility coefficient. The chief limiting factor was found to be the content of the saturated fatty acids with 18 or more carbon atoms. The relationship between melting point of the fat and digestibility was determined to be a reflection of the content of saturated fatty acids. Human infants utilize only a fraction of the saturated fatty acids while the adult human utilized these better than does the rat.

KNIGHT, A. A. AND MILLER, J.: *Comparative studies on the iodine absorption of anayodin, chiniofon, diodoquin, and vioform in man.* (Proceed. Central Soc. Clin. Res., V. 20 p. 75, Nov. 1947).

The absorption of the oxyquinoline drugs was studied indirectly by measurement of blood iodine levels. Iodine determinations were made before and on the third, seventh, and tenth day following oral administration of the drugs. Vioform was the most readily absorbed. In terms of the recommended therapeutic dosage of each of the drugs, the diodoquin showed the highest absorption levels of iodine. Absorption of each drug was uniform, being highest on the seventh day. The drugs were not toxic. They probably do not destroy cysts but prevent cyst formation by destroying the trophozoites.

BASU, U. P., MUKHERJEE, S., AND BANERJEE, R. P.: *Influence of bile salts on the absorption of quinine.* (J. Amer. Pharmaceut. Assoc., (Sci. Edit.), V. 36, p. 266, 1947).

The interaction between bile salts and quinine and the relation of this interaction to the absorption of quinine from the intestinal tract were studied. The colloid formed by this interaction was dialyzable and the conclusion was drawn that this may explain the mechanism of quinine absorption. It was suggested that more effective absorption from the intestine may be obtained by administering bile salts with the quinine.

MISCELLANEOUS

BAUER, C. W., AND WILSON, E. E.: *Lipolytic activity of pancreatin U. S. P.* (J. Amer. Pharmaceut. Assoc., (Sci. Edit.), V. 36, p. 109, 1947).

Titrimetric determinations of fatty acids liberated from an olive oil substrate were made, using pancreatin as the source of lipase. The addition of bile salts and albumen to stabilize the digestion mixture was found undesirable because of the introduction of color or of a source of acid which is not fatty acid. An inert emulsifying agent, such as bentonite, is preferred. A well-buffered digestion mixture, using ammonium hydroxide-ammonium chloride, is essential. The use of ether to remove undigested olive oil is recommended since ether does not interfere with the lipolytic activity.

DANIELSSON, C. E.: *Molecular weight of alpha amylase.* (Nature, 160, 899, Dec. 27, 1947).

The alpha amylase studied was crystallized by Prof. Kurt Meyer from pig's pancreas. Determination of the molecular weight was made by both diffusion and sedimentation methods. The crystalline enzyme was dissolved in pH 8.4 borate buffer. The molecular weight was calculated to be 45,000.

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